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INTESTINAL DIVERTICULA¹

By E. I. SPRIGGS AND O. A. MARXER

From Ruthin Castle (Duff House)

With Plates 1-9

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Introductory.

IN the course of the last thousand consecutive X-ray examinations of the alimentary canal, residues of barium have been detected in intestinal diverticula in 143 patients. This frequency is much greater than that formerly described by ourselves (31) and others—the increase in the figures being due to improvement in technique. Diverticula may occur in any part of the intestine, but in most cases they are found either in the duodenum or the colon, the affection having different anatomical and clinical characters in the two regions.

¹ Received September 8, 1925.

We use the term diverticulosis, as proposed by one of us some years ago, to embrace all phases of the disease. The pouches often exist over long periods without giving rise to recognizable symptoms. This state we call quiescent diverticulosis. When infection or inflammation occurs in the pouch or pouches, and particularly in the small multiple colonic diverticula, involving the peritoneum or other structures near by, the condition is one of diverticulitis; this may, if persistent, be followed by a further stage of hypertrophic change, when the elasticity of the bowel wall is lost, with thickening, rigidity, or tumour. Increasing experience has shown that not only the frequency of diverticulosis, but also the proportion of cases in which diverticula, duodenal, jejunal, or colic, give rise to symptoms of disease, is greater than appeared likely from earlier studies.

Two years ago one of us (O. A. M.), in describing the X-ray aspects of diverticulosis of the large bowel (52), showed that a pathological condition can be recognized in areas of the colon before diverticula are found. This we call the prediverticular state. It is now as familiar in radiological examination of the colon as the quiescent diverticula are to the morbid anatomist, or as the inflammatory hypertrophic stage of diverticulitis is to the surgeon.

I. DIVERTICULA OF THE SMALL INTESTINE.

Historical.

Chomel (4) is often referred to as the earliest recorded observer, in 1710, of a duodenal pouch, and, after him, Morgagni, in 1761 (22). The references are discussed in a former paper (31), and reasons given for doubting whether the sacs mentioned by these observers were of the same nature as those here described. Soemmering, in 1794 (30), mentions a pouch of the small intestine, which may, however, have been a Meckel's diverticulum.

In 1815 Fleischman (10) gave an excellent description of the post-mortem appearances in three typical cases. In one the bile-duct opened into a round, bladder-like pouch, the pancreatic duct opening into another side of it. The walls were thinner than those of the intestine, and no muscle fibres were to be seen except a ring of them at the base. In the second case the bile-duct opened into one pouch, and there were three others near by. In a third there were four pouches. Fleischman used the term 'Divertikel', and pointed out that the pouches were often found about the region of the biliary and pancreatic ducts, but might occur away from them, and were rare in the jejunum. He suggested as a cause strong and frequent distension with food, drink, or air. He described also the occurrence of diverticula, usually single but sometimes multiple, in the large intestine, mostly at the mesenteric side, and discussed at length the origin of diverticula and their division into true and false. Cruveilhier (41) was apparently unacquainted with Fleischman's description, for, although giving a good account in 1849 of diverticula of the oesophagus and the large intestine, he states that the digestive tract between is exempted.

Habershon (14), in this country, referred to duodenal diverticula in 1857. A

specimen was also described by Norman Moore in 1884 (21). The first detailed description that we have found, however, after that of Fleischman, is in the paper by Perry and Shaw (24) which appeared in 1893. These writers gave a careful account of non-inflammatory pouches, based on fourteen post-mortem examples. Letulle, in 1898 (18), described a case with views of the aspect from the mucous surface which have been reproduced by various writers since; one of them is shown in Pl. 1, Fig. 1. It is taken from the inner surface of the duodenum, and shows a group of diverticular orifices neatly arranged round the duct aperture of the ampulla of Vater. The ampulla itself gives the appearance almost of prolapse.

Subsequent papers of interest are those of Fischer (1900) (9), Voigtel (1904) (35), and Gordinier and Sampson (1906) (13). The last-named authors, writing in pre-X-ray days, emphasize that acquired diverticula of the small and large intestine are more frequent and more often the cause of symptoms than the number of reported cases and post-mortem records show. They describe a case associated with symptoms, as did later Rosenthal (27), Bauer (2), and Basch (1). Buschi (4), of Bologna, in 1911, collected fifty-four cases of which exact accounts were available, including three of his own. He referred to sixty-two previous authors, including Rolleston and Fenton (1901) (26), and Keith (1903) (16). Two years later, D. P. D. Wilkie (36) wrote a good summary, with fresh cases and excellent illustrations of post-mortem specimens. In 1917 Ritchie and McWhorter (25) had found seventy-six cases in the literature and published a radiogram of a case under their care. They mentioned that eleven others had been reported by radiologists, some of which had been verified at operation. Davis, in 1913 (8), thought that in only one case of sixty-one were there symptoms for which a diverticulum may have been responsible. In 1914 Linsmayer (19) gave an account with good pictures of forty-five cases found in 1,367 post-mortem examinations. No symptoms had been recognized as associated with the condition, but he states that whilst the pouches had hitherto been regarded as harmless, in most cases disturbances were present.

The first published case of a duodenal diverticulum described by X-rays and confirmed by operation appears to be that of G. Forsell, which was examined on May 1, 1914, and operated upon on May 14, by F. Key. This case was published in Swedish in October 1915 in a volume of the *Nordiskt Medicinskt Archiv*. It was reported in German in 1916 (12). Dr. J. T. Case had recognized pouches with X-rays in 1913, which were explained by operation,² and published an account in 1915.

Radiological evidence had now begun to accumulate, and in 1920 three papers appeared in which the subject was treated from an X-ray point of view, namely, our own short study of ten cases, with photographs, already referred to (31), in July, a valuable and comprehensive paper by J. Case in November (6), and an excellent paper by Clairmont and Schinz (7). The last-named authors described six cases; all had symptoms, and in five the pouch was the cause. Two

² Private letter.

were treated surgically. They say that pouches in the first part of the duodenum may, as noted by former writers, arise from ulcers or scars, but that pouches lower in the duodenum have a different origin; and that duodenal diverticula may be a source of danger and therefore a surgical indication.

J. Case described the largest series published hitherto by one observer. He found diverticula of the duodenum in 85 out of 16,847 complete barium meals, about $\frac{1}{2}$ per cent. In 5 the diagnosis was confirmed by operation. His figures illustrate the general findings that in most cases (78 out of 85) the pouches are single, that the second part of the duodenum is the commonest site, that women are rather more liable than men (60 per cent. in females), and that the condition is usually found in later life. The average age of his cases was 56. In some inflammatory symptoms arose, surgical treatment was advised, and in a few carried out. The patients were generally sent with a diagnosis of duodenal ulcer, gall-bladder disease, or chronic pancreatitis. Barium sulphate, in drachm doses three times for one day each week, is suggested as medical treatment.

Ohnell, in 1923 (23), described 34 cases (20 women, 14 men), excluding pouches of the first part of the duodenum, as these may have arisen from ulcers. In this paper the symptoms were carefully analysed and discussed, and in several the complaint was thought to be caused directly or indirectly by the diverticulum, a simple diagnosis of duodenal diverticulum being made in 10 out of the 34. There were but few (15 per cent.) who did not complain of 'pain' or 'burning'. Other symptoms were vomiting, eructation, and, less frequently, diarrhoea, or constipation. In 10 there was pain on pressure over the diverticulum. Ohnell suggests, from the frequent association with other lesions, that duodenal diverticula predispose to complications in the duodenum and the alimentary canal generally. He thought that his cases did not show ground for radical operation. For medical treatment it was suggested that all food should be minced, with the idea of preventing such objects as fish-bones getting into the pouch.

Various other observers, whose papers we have consulted, are mentioned in the list of references.

Incidence.

In the last 1,000 consecutive radiological examinations of the alimentary canal duodenal diverticula have been detected 38 times. In 32 of these patients the diverticulum was single; in 6 patients two or more were present, 1 patient having six duodenal diverticula as well as several in the jejunum. In a number of other cases a small shadow was seen internal to the second part of the duodenum which could not be distinguished from the appearance of a small residue of barium in the ampulla of Vater. Reasons are given below for thinking that some or most of these shadows were due to incipient diverticula, but they are not included in the series.

In all, 51 duodenal pouches were recognized in the 38 patients concerned, 1 arising from the first part of the duodenum, 30 from the second, 16 from the third, and 4 from the fourth part. Twenty of the patients were women and 18 men.

The average age was 55, the youngest being 20, and the oldest 75. There were 2 under 40, 7 under 50, and 15 between 50 and 60 years of age.

A typical duodenal pouch is shown in Pl. 1, Fig. 2. An account of this case (No. 2,885) is given below (p. 12) under the heading of Symptoms.

Method.

The routine method of observing the different aspects of the duodenum on the screen, and of obtaining accurate photographs, as described by one of us (52), is all that is needed to detect, and obtain good photographs of, diverticula. The opaque meal used in all these cases consisted of 120 grm. of barium sulphate suspended in 500 c.c. of buttermilk. No special technique is necessary, except that the diverticulum must be brought into view and its various profiles shown either by rotation of the body or shiftings of the tube.

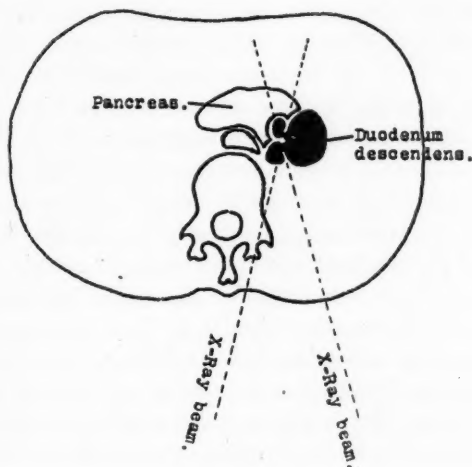


FIG. 3.

Fine detail cannot, of course, be made out on the screen, and a series of short-exposure films is often required, taken at different angles, to obtain the delicate shadows that show the connexion with the gut.

Fig. 3 shows schematically the angles from which views may need to be taken in order to locate the mouth of a diverticulum, and to determine its relation to the duodenum. For example, Pl. 1, Fig. 4, which was taken in the supine position, may be compared with Fig. 5, from the same patient rotated to the left. It will be seen that in Fig. 4 the large diverticulum is separated from the duodenum, whilst in Fig. 5 it is superimposed upon it, whereas the smaller one is now in better profile. The apparent displacement in the second picture, taken after rotation, shows, as will be seen by a reference to Fig. 3, that the large diverticulum lies behind and the small one more to the front of the duodenum.

The existence of an accessory pocket may be regarded as proved if it can be seen and recorded on a film, both during the passage of barium and at a later stage, as an opaque residue after the gut from which it arises is empty. It is desirable also to determine how long the pouch retains material after the last of the opaque meal has left the duodenum. In certain cases more information may be required, and in such a stereoscopic pair of films is sometimes of value.

If precautions are not taken, small opaque spots in the mucous folds of superimposing jejunal coils may be mistaken for accessory pockets. Such coils can generally be displaced by manipulation. Further, the diverticulum will retain its contents or fill repeatedly during the transit of the meal, whereas the jejunum will pass on its contents.

Aetiology.

Authorities have thought that most of the pouches are congenital in origin, and in support the following points have been put forward: There is often no evidence of inflammation, dilatation, or hypertrophy of the adjacent bowel; the inner concave aspect of the horseshoe-shaped duodenum, from which most pouches arise, is, according to these writers, supported by the pancreas, and should be less liable to extrusions from weakness of the wall than the convex aspect; in some pouches the mucous membrane at the apex is thrown into folds (Grey Turner), which seems to make it unlikely that these are herniae from internal pressure; the pouches are frequently single; the development of the pancreas and liver as outgrowths from this part of the embryonic gut suggests that other outgrowths are not improbable; pancreatic tissue may be found in the wall of a pouch, and in many the distal pole lies in or close to the pancreas; lastly, other congenital anomalies, such as folds of the duodenum (Wilkie), Meckel's diverticulum, oesophageal diverticula, and sclerosis of the duodenum (E. Shaw) may coexist. But it may be noted that in congenital stenosis of the small intestine, although the bowel above the obstruction is commonly dilated, pouching of this type is not usually recorded (N. I. Spriggs).

The alternative view is that duodenal pouches are caused by extrusion of parts of the bowel wall which are weak naturally or are made so by ulceration or other pathological processes. In favour of extrusion from internal pressure as a cause of non-inflammatory diverticula, Perry and Shaw point out that the duodenum is the only part of the small intestine in which ulcers produce pouches, and suggest that the closure of the pylorus when the duodenum is contracting will cause a higher pressure than is likely to be produced elsewhere in the small intestine. This is borne out by observing the duodenum on the X-ray screen; frequent and strong waves of contraction occur in this part of the bowel. Ulceration is common in the first part of the duodenum, and pouches in that region, which are infrequent, are suspected of arising from them. Most pouches, however, are found in the second and lower parts, which are not prone to ulceration.

Against the congenital view may also be noted the following: The situation of the pouches on the inner aspect is ascribed to weakness there from the entrance of blood-vessels and of the ducts, close to which most of the diverticula arise, also from lack of peritoneal support; with such an acquired extrusion, no inflammatory phenomena or hypertrophy of the neighbouring bowel would be expected. Pancreatic tissue is sometimes found in the wall of the duodenum and might be carried along into the wall of the pouch. An argument of weight is that nearly all duodenal diverticula have been found, either radiologically or *post mortem*, in elderly people.

No one would deny that congenital pouches may, and do, occur, but a study of more cases lends support to the view, which in our former paper was discussed with favour rather than advocated, that most of them are acquired in later life. It is, of course, arguable that although the recognizable pouch may arise in adult life, yet a congenital defect was present from infancy which permitted or conditioned its beginning. To this a complete reply can hardly be given. But it is clear that the typical duodenal pouch is rare in the young, but not infrequent in the old, and that it can be seen after middle age to increase from a very small to a considerable size.

We shall offer evidence below that the multiple colic diverticula are preceded by a local condition, probably of an inflammatory nature. It is possible that in the duodenum also, not only anatomical weakness, but local catarrh, short of ulceration, may predispose to the beginning of the extrusion. Once formed, the pouch, which has little or no muscle in its walls, would be distended gradually from recurring rises of intraduodenal pressure caused by the contractions of the filled gut after each meal.

It may be noted that very few of these patients had entirely normal tooth surroundings, and obvious oral sepsis was present in thirteen cases, i.e. 34 per cent. Gall-stones were found in six of the thirty-eight cases, or 17 per cent. A test-meal was given in nineteen cases, and in only three of these was the amount of hydrochloric acid less than normal.

Developing Diverticula.

In recent years, with improvement in method, we have seen many sacculi at an early stage of formation, the smallest pouch having been in the youngest subject in the series, who was aged 21. In others a minute pouch might be seen beside a well-developed one, as in Pl. 1, Fig. 6. In this patient (♀, aged 48) a collection of diverticula appear to be forming round the papilla, similar to those in the illustration from Letulle shown above (Pl. 1, Fig. 1). Sacculi of the jejunum were also seen. Neither these nor those of the duodenum had been detected six months earlier, or at an examination by another radiologist a year before that.³

³ Since going to press we have re-examined this patient after a year's interval. In that time the smallest pouch has doubled its size. The larger one has not increased.

In two patients we have had an opportunity of re-examining the duodenum after a long interval. In the first (σ^7 , aged 50) the shadow was recorded as arising from the ampulla of Vater, and as being of the size of a cherry-stone. Eight years later a pouch could be seen, whose vertical diameter measured $1\frac{1}{2}$ inches, containing opaque food, air, and secretion, as shown in Pl. 2, Fig. 7. In this patient, discomfort, which was intermittent, could be located to the pouch, radiating to the left on a level with the pancreas. The diverticulum contained a residue four hours after the opaque meal was taken, but soon after emptied readily, presumably owing to its wide mouth.

3½ hours. Supine.

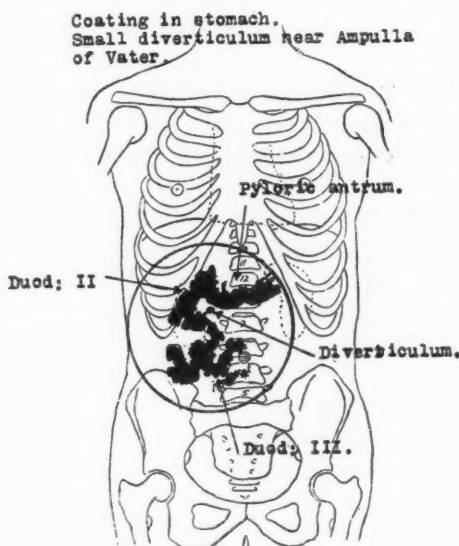


FIG. 8.

The second patient was a man of 51, the subject of gastro-enterostomy for former gastric and duodenal ulceration. At the first examination an opaque spot was seen of the size of a pea: we had at that time recently observed a case of chronic perforation of a duodenal ulcer which had not reached the peritoneal cavity, and, being then unfamiliar with incipient diverticula, suspected that condition. The shadow was, however, not near the first part of the duodenum, from which the pouches formed at a site of ulceration usually arise. A drawing of the radiogram, made at that time, is shown in Fig. 8. On re-examination four years later, a developed diverticulum was seen in the neighbourhood of the ampulla of Vater. Intermittent discomfort was complained of and severe pain was caused by pressure over the pouch. It measured 18 mm. across the base (Pl. 2, Fig. 9) and had grown at the average rate of 3 mm. a year. If it may be supposed that the diverticula had increased at a similar rate throughout in these

two cases, they would have existed from four to ten years before the first observations were made. In the case of the first patient the symptoms dated back six years before the earliest examination.

Further evidence is furnished by a woman whose age was 69. Pl. 1, Fig. 4, already referred to, shows a diverticulum of medium size of the second part of the duodenum, and below it is a smaller one. In Fig. 5, a right oblique view, its long narrow neck can be seen. If this pouch had existed throughout life it would be expected to be larger after so many years. It is far more probable that it is of recent origin.

Small Shadows.

We have often seen small shadows near the ampulla of Vater and have thought that they were caused by opaque food in the papilla. But since we have been able to re-examine, after a long interval, the patients mentioned in the last section, we are inclined to regard many of these as incipient diverticula, especially as it is not easy to determine the site of the papilla in any given case. It is unlikely that the papilla will admit food as a rule unless the orifice is gaping from some pathological cause, such as the presence of a stone near by. We have published (52, p. 106) a photograph of such a bile-duct admitting barium; the basal border of the apparent diverticulum was ragged in outline from an inopaque calculus. Sharp pain was produced on pressure at that place.

Diverticula from the First Part of the Duodenum.

The duodenal cap is a frequent site of ulceration, and such ulcers may, though not usually, show a crater which simulates a pouch, or an actual pouch may arise from the base of an ulcer; a chronic perforation which has not reached the peritoneum may also cause confusion. Ohnell has evidently met the same problem, for he states that it is difficult to distinguish diverticula from perforating ulcers radiologically, and on that ground excludes all accessory pockets of the first part of the duodenum from his paper. This seems to go a little far, for Perry and Shaw (24) found seven duodenal diverticula in the first portion out of fourteen cases, the mucosa being intact in all. In this series there is only one pouch of the first part of the duodenum.

A Diverticulum on the Outer Border of the Duodenum.

Nearly all pouches arise from the inner concave aspect of the duodenum, probably because the vessels and ducts enter there and there is no peritoneal covering. Pl. 2, Fig. 10 (♀, aged 69) shows a large pouch arising on the free outer border about five inches from the pylorus. It appears to be segmented in the middle, perhaps from a crossing blood-vessel; there is also a deformity of the distal part of the duodenum. The general appearance simulates that of a fistulous

opening into the gall-bladder; but on moving the tube 10 cm. downwards it became clear that the pocket lay behind as well as above the duodenal summit. Moreover, the orifice showed a normal plication (Pl. 2, Fig. 11), with no evidence of constriction, the mouth measuring nearly one inch.

Diverticula of the Second, Third, and Fourth Parts of the Duodenum.

The second part is the commonest site. Thirty out of the fifty-one pouches observed in this series were situated there. Pl. 1, Fig. 2 gives a characteristic appearance. This pouch has a wide mouth and, judging from an oblique view, lies behind and outside the pancreas. Sometimes a pouch may be seen to be flattened against the pancreas, but frequently diverticula lie in the pancreatic tissue. Pl. 3, Fig. 12 shows three or four pouches or a loculated pouch in this position.

Pl. 2, Fig. 13 is a photograph of the largest pouch in this series. Its vertical diameter is four inches. The indentation on the duodenal border is, we believe, caused by the common duct. Pl. 3, Fig. 14 shows an oblique view, from which it be noted that the second part of the duodenum is slightly displaced forward. Fig. 15 shows the diverticulum at eight hours after the meal, the stomach having emptied three hours earlier. There was great retention in this pouch; it contained an opaque residue seventy-two hours after the meal, when the rest of the alimentary tract was clear.

Diverticula arising from the third part of the duodenum are shown in Fig. 16 (♂, aged 59). The view is a right oblique one, taken half an hour after ingestion. There are three pouches of different sizes: one is near the ampulla of Vater, another, the longest, in the middle of the third part, and one of medium size is at the jejunal flexure.

Pl. 4, Fig. 17 shows a large typical mushroom-shaped pouch of the fourth part. There were also small multiple diverticula of the ileum and the colon. The patient was a man of 53, the subject of chronic appendicitis and mitral regurgitation.

Jejunum.

Diverticula of the jejunum were observed in seven patients. In four of these there were also pouches in the duodenum. Pl. 3, Fig. 18, a left oblique picture (♀, aged 54), taken at 1½ hours, shows one just beyond the duodenojejunal flexure, and a large one farther on. There is also a typical extra-pancreatic duodenal pouch, seen in its narrow profile, and showing the contact outline with the pancreas.

Ileum.

In this part of the gut (excluding Meckel's diverticulum) we have hitherto only found small diverticula varying from a mere pin-head projection to the size

of a lentil. These we have seen seven times. They do not appear to be of the same kind as the large pouches we have been discussing, but are like the early stage of multiple colic diverticulosis.

Pl. 4, Fig. 19 (♂, aged 61) shows the X-ray appearance, which is new to us. Near the uppermost diverticulum are the convex impressions which are ascribed to prediverticular disease. For such delicate appearances in an active bowel instantaneous photographs are needed; and some of the detail has been lost in the reproduction. In the negative the spines appeared more feathery and looked rather more like fluff than the characteristic and neat prediverticular deformity of the colon, to be described below. There were a number of well-developed diverticula in the terminal ileum, about eight or ten inches from the ileo-caecal junction. Those nearer the caecum are more recent and the smallest. This supports the view that the adjacent feathery appearance is a prediverticular condition, especially as there was in this case a prediverticular state and some small diverticula of the colon.

Three other cases with small ileal diverticula also showed multiple diverticula in the colon.

Appendix.

Diverticulosis of the appendix occurred six times. The successful demonstration of the pocket, as in the colon, depends on the angle of observation. The diverticulum may lie behind, in which case it would show as an increased density, circular in shape, or it may be superimposed in varying degree. The same effort should be made to show a bulge in profile in the appendix as in the colon or elsewhere.

In one case a diverticulum of the appendix, and one of the transverse colon, were the only ones found in the alimentary tract. In the others there was a diverticular colon, in one case the diverticulosis being confined to the caecum. In one there were duodenal diverticula.

Pl. 4, Fig. 20 (♂, aged 48) shows a retro-externo-caecal appendix. An accessory pocket can be seen beneath the summit. The apex of the caecum is turned up posteriorly.

Symptoms.

In our former paper the opinion was expressed that 'as a rule duodenal diverticula are harmless, no doubt because they drain easily from the wide openings. The fact that their existence has generally been revealed accidentally after death bears witness to their innocent nature.' Particulars were then given of a few cases in the literature and one of our own, which appeared to be exceptions, as they were associated with symptoms. The study of a larger series in the last five years has shown, however, that the condition is not so harmless as then appeared, and that it is by no means exceptional for duodenal and jejunal diverticula to give rise to definite and sometimes distressing symptoms.

The following cases may be quoted as examples:

No. 2885, ♀, aged 66. Eight months' history of discomfort in the epigastrium about an hour after food. Nausea in the night, vomiting bile in the morning, flatulence. The fractional test-meal gave a normal gastric juice, but slow emptying, as of duodenal irritation. There was a diverticulum of the second part of the duodenum, which was tender (Pl. 1, Fig. 2). No other lesion was found in the alimentary canal or elsewhere. The symptoms disappeared with suitable treatment.

No. 2112, ♀, aged 69. Discomfort and an irritable feeling amounting to pain in the epigastrium at odd times; woke patient at night. Occasional nausea. There were three diverticula, probably connected with the second part of the duodenum. There were also small multiple diverticula of the colon, and constipation. With treatment the discomfort and nausea disappeared. Pain was much less, but was occasionally felt.

No. 2433, ♀, aged 75. Thirty years' history of indigestion. The patient had been operated upon three years before for strangulation of bowel. Now pain in the upper abdomen on waking, eased by food. Also a tearing pain two to three hours after food, leaving a sore feeling in the epigastrium. Also pain in the left flank, worse after motoring. Achylia. A very large double pouch (see Pls. 2 and 3, Figs. 13, 14, and 15), which retained material seventy-two hours, was connected with the second part of the duodenum. There were multiple small diverticula of the splenic flexure which were probably the cause of the pain in the left flank. Operation not advised on account of great improvement with treatment, and of age.

No. 1424, ♂, aged 54. At least seventeen years' history of attacks of nausea and vomiting, discomfort in the lower abdomen $\frac{3}{4}$ hour after food, diarrhoea. Haematemesis three times. There was a double pouch, or two pouches, of the second part of the duodenum. Subacid gastric juice. There was no X-ray or faecal evidence of colitis. Recovered with treatment. 2 $\frac{1}{2}$ years later wrote had kept well.

In these four cases symptoms were definite and no adequate lesion was found to explain them except the duodenal pouches, which were also definite.

Out of the present series of 38 cases, in 18, i.e. 47 per cent., the symptoms complained of were, after a careful investigation, clinical, radiological, and chemical, attributed to irritation from the duodenal pouches. In 10 cases the symptoms were indefinite. They were possibly, in some probably, caused by the pouch, but, in part at least, could be explained by other lesions. In the remaining 10 cases, 26 per cent., there was no ground for thinking that any abnormal signs or symptoms arose from a pouch.

In the 18 patients whose symptoms were judged to be due to the diverticula the complaints were as follows:

12 had *flatulence, fullness, distension*, or a heavy or a tired feeling about the epigastrium coming on after food. In 8 of these a definite time was given for the onset, varying from $\frac{1}{2}$ hour to 2 to 3 hours after food. In 1 only was more food

said to give relief. In some the discomfort was localized to the diverticulum. One other complained of a boiling feeling in the abdomen, but was free from this for long periods.

Pain or aching was complained of in 6 patients.

There was *nausea* in 6 patients, with *vomiting* in 3, and *haematemesis* in 2 of them.

Three patients had *loose motions* and 2 were *constipated*.

One patient complained of headache and 1 had had jaundice. One had pain in the back, possibly arising from the pancreas.

In 5 patients a diverticulum was tender.

The association of a pouch with loose motions and pain in the left lower part of the abdomen must be mentioned. There is reason to believe, from observation of two of the cases, that colitic symptoms can be caused by putrefactive material from a duodenal diverticulum.

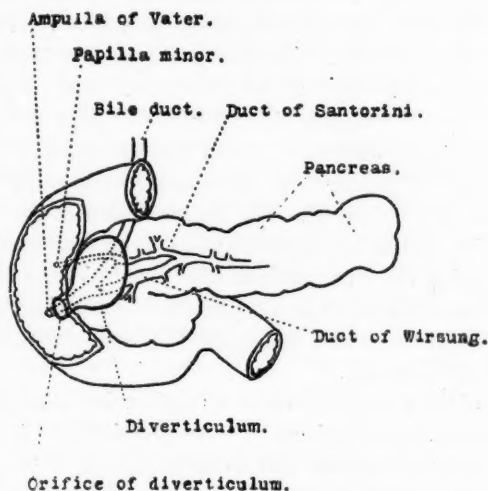


FIG. 21.

The cause of the symptoms is probably mainly stretching of the walls of the pouch by distension with food, or irritation by either acid or putrefying material. Irritation of the duodenum by a pouch or its escaping contents is illustrated by one of our cases in which the second part of the duodenum contracted persistently as a whole below the opening of a small diverticulum. The active movements of the bowel may also drag upon a taut accessory pocket in a region sensitive to tension or pressure.

A pouch distended by active contraction of the bowel may also press on surrounding structures. Fig. 21 shows a scheme of the anatomy. A large diverticulum may compress the duct of Santorini, if it arises in front of the opening of the common duct; or the common duct and the duct of Wirsung, if it arises behind.

Treatment.

In these cases medical treatment has been directed to aid the pouch so far as possible to empty itself, and thus prevent or diminish putrefaction of its contents; to lubricate it and to disinfect its contents; to correct or relieve any accompanying disorder; and to raise the tone of the alimentary canal and the body generally. The results will be reviewed below, but we may remark here that the benefit derived from medical treatment has been much greater than was expected from an *a priori* consideration of the anatomical condition and the symptoms:

When the length of time that opaque material is retained in a pouch after the adjoining bowel is empty has been ascertained, it is often possible to show with another barium meal that a pouch empties much more quickly if the patient lies in a particular position. A pouch of the second part of the duodenum, for example, may discharge its contents more easily if the patient lies on the right side. In No. 2433, for instance, described above (p. 12), who had the largest pouch we have seen (Pls. 2 and 3, Figs. 13, 14, and 15), the emptying was much aided if the patient lay on the right side. Such a patient would be directed to lie in the prescribed position for half an hour or an hour just when the main part of the food would be leaving the duodenum, usually about three hours after a meal. In practice this time would often coincide with the hour immediately before the next meal. The determination of the best position and of the time at which it should be assumed will depend upon accurate radiological observations, including the demonstration of the mouth of the diverticulum.

For lubrication of the pouch liquid paraffin is given night and morning. If the bowels are loose the dose may be reduced to a teaspoonful, but the patient is advised to take it permanently.

Disinfection of the alimentary canal by antiseptics taken by the mouth has often been attempted, but is seldom if ever practicable. A duodenal pouch, however, lies so near the stomach that an antiseptic can be reasonably expected not to have lost its power. We prescribe as a rule a capsule of kerol three times a day two hours after food. This also is continued permanently, except that it is left off for a day or two at regular intervals to avoid any possible poisoning effects, for coal-tar derivatives may do harm if given too long. The frequency and length of the intervals is prescribed after the case has been observed for a time. Many patients can take kerol continuously with an interval of two or three days in a fortnight.

Distension and discomfort after food may sometimes be relieved in these cases by such usual remedies as cream of magnesia or a carminative mixture. Patients with achylia receive an acid drink with the chief meals.

The diet should be plain and well cooked, avoiding condiments and any foods which are known to disagree. In some patients greens and fruits are omitted, but these foods can generally be borne if given sieved or puréed. In cases with constipation it is often possible to give a full anti-constipation diet,

including salads. If the food is well prepared and masticated we doubt if any particular foods or particles are likely to do harm from retention in a pocket, as is suggested by some writers.

Regular exercise is taken, sleep secured, and any other measures which may be called for in the individual case are prescribed.

The pockets can seldom, if ever, be emptied by manipulation, and if there is any tenderness or evidence of irritation it is better not to massage the upper abdomen at all.

Results.

In thirteen of the eighteen patients whose complaints were due to irritation from duodenal pouches the symptoms were completely allayed by a few weeks of medical treatment. The patients are told that the period of treatment is to be spent in finding out, so far as possible, what measures do good. They then carry on the prescribed régime at home under the supervision of their own doctors.

Of the five other patients three were relieved, two of them greatly; one who had duodenal and jejunal diverticula lost the flatulence, nausea, and regurgitation of food from which she had suffered, but a pain in the back, which was thought to arise from implication of the pancreas, was unaltered.

The case of the remaining patient, No. 1571, who was operated upon, must be referred to in detail: A man of 54 complained of nausea, with occasional vomiting, and attacks of diarrhoea. He had brought up blood three times in twenty-three years. Six or seven diverticula of the duodenum and three of the jejunum could be made out. Pl. 5, Figs. 22 and 23 show a maze of air-spaces and levels of fluid secretion and of opaque food. The gastric juice contained no free hydrochloric acid, and suitable treatment for achylia, especially the administration of acid, gave much relief for a time. Vomiting recurred, however, and in 1921 gastro-enterostomy was performed. Figs. 24 (duodenum) and 25 (jejunum) show the condition found at the operation. All but the postero-internal diverticula were traced. Three were seen in the second part of the duodenum, three or four in the third part, and three in the proximal jejunum. The largest pouch occupied the head of the pancreas; it showed a cicatrix at its mouth. Those in the proximal jejunum showed no evidence of former inflammation. After operation some nausea was complained of for a year, but now, four years later, it is rare. He has no other symptoms and follows an active life of work and recreation.

Surgical treatment would probably benefit greatly some of the patients who cannot be relieved by the measures above detailed, and particularly those with multiple diverticula and those with a large and increasing pouch.

In some, gastro-enterostomy would probably lead to cure as in the case above mentioned. In others it would be possible to excise the sac, although not in the frequent form which lies embedded in the pancreas. Sir Harold Stiles, in a letter of May 24, 1922, described to one of us the removal of a diverticulum $2\frac{1}{2}$ inches long from the duodenum. 'It was the size of a hen's

egg, and the fundus of it presented between the stomach and the colon, covered by the upper layer of the transverse mesocolon. The neck, which admitted the forefinger, sprung from the region of the opening of the pancreatic duct, and the wall of the diverticulum contained small areas of pancreatic tissue. The muscular coat ended abruptly at the neck.'

Diverticula are easily missed when the abdomen is opened, as they are extraperitoneal. We have known a pouch four inches in diameter remain undetected. But the surgeon should not fail to find a large diverticulum if it has been defined by X-rays; we suggest that the mouth, which is seldom narrow, should be palpable, and that the opposite bowel wall may be intussuscepted into it by the finger if its situation is known.

Many of the patients are past the period of active life; and in two of our series who might have been benefited by surgical treatment of the pouch, age and other infirmities made an abdominal operation inadvisable.

II. DIVERTICULA OF THE LARGE INTESTINE.

Introduction.

Diverticula of the large intestine are commonly small and multiple, differing in both these respects from the usual form found in the small intestine.

As in the case of the duodenal pouches, improved technique and more thorough search has shown that, first, colic diverticula are much commoner; secondly, that they are more often associated with symptoms; and, thirdly, that these symptoms are more amenable to treatment than was recognized when our former note was published five years ago (60).

When the pouches have reached the size of a small currant they are seen, after a barium meal or enema, upon the radiogram, as extrusions from the normal outline of the bowel wall. They retain material longer than the main lumen of the gut, and are then obvious as a chain of opaque dots lying along the course of the empty bowel. Pl. 4, Fig. 26 shows such residues lying in the pockets. It was taken 120 hours after the barium meal and 24 hours after the rest of the barium had left the bowel. Pl. 6, Fig. 27 shows the appearance of diverticula after a barium enema.

We shall bring forward evidence to show that, whatever may be the pathology of the duodenal pouch, in colic diverticulosis we are dealing with a disease, and not, except as a secondary phenomenon, with a mere passive extrusion.

Historical.

The classical study of Telling and Gruner, 1917 (62), which was undertaken at the instance of Moynihan, contains a full bibliography of this subject. They summarize their historical researches by saying that 'diverticula have been noted

by various observers for more than a century, but for the most part as isolated cases . . . the condition was looked on as a rare pathological "curiosity" of no real clinical importance'. Telling and Gruner continue: 'This aspect of diverticulum-formation in the large bowel (particularly in the sigmoid flexure) was first given prominence by Graser in 1898, who showed that such cases are not very uncommon, and are of great importance. In particular he described the hyperplastic stenosing type known as peridiverticulitis, and its simulation of carcinoma of the sigmoid flexure. Shortly after this the subject was extensively studied in America, where Beer (37), Fischer (43), and others made contributions to the aetiology, and the Mayos (54, 55), Wilson (64), Brewer (39), Giffin (47), and others to the clinical aspects; also Patel (57) in France (especially in regard to sigmoiditis and the acute types of the condition) and Moynihan in England. The last observer published the first case (1907) in this country of peridiverticulitis causing a "mimicry of carcinoma", and moreover laid very special stress on the role of the diverticulum in causing non-malignant vesico-sigmoid fistulae' (56). Dr. Telling's first paper on this subject appeared in 1908.

Another pre-X-ray paper is that of Gordinier and Sampson already referred to (48), who described diverticula of the large intestine and the main features of diverticulitis.

Multiple colic diverticula were mentioned by Fleischman in 1815 (44), but the first good account we have found in the earlier literature is that of Cruveilhier in 1849 (41). He described, in old people who are the subject of constipation, between the longitudinal bands of muscle, a series of small pisiform tumours, dark-looking like varices, their colour being due to hard faeces contained in the cellules which are often buried in fat and therefore escape an inattentive observation. 'I have never found more of these than in the body of Professor Alibert. He had several hundreds of them, all having a distinct orifice, usually narrow.' He saw the 'cellules' in the lower part of the large intestine only, and ascribed the predilection for that part to the unequal resistance of the stools, the longitudinal fibres being in three parallel bands with relative weakness between them; the faeces also remained longer and became harder there, and the efforts of defaecation would be particularly likely to cause this kind of displacement. 'One conceives', he goes on, 'that these little mucous cellules can be irritated by the presence of faecal matter and become the seat of inflammation and perforation.' To this description of Cruveilhier but little has been added. His words are almost reproduced in a recent letter to one of us describing diverticula which were seen at an operation, although their nature was not recognized.

Of recent papers we would refer especially to those of J. W. Keefe in 1917 (50), D. Roberts in 1918 (58), and a contribution of our own to a discussion at the Royal Society of Medicine opened by Dr. Telling in 1920 (60). Up to that time the absence or scantiness of accurate radiology had confined the attention of clinicians almost entirely to 'surgical' diverticulitis with symptoms of peritoneal involvement and an inflammatory mass in the left iliac fossa. We called attention to a small series of cases of established multiple diverticula in which such symptoms and

complications were absent, and suggested the term diverticulosis for that condition, the term diverticulitis being reserved for the stage at which diverticula had become inflamed.

Enfield, in 1924 (42), reports that, in 1.2 per cent. of cases at Battle Creek, colonic diverticula were discovered incidentally. He thought that in about half there were no associated symptoms. In others there were vague disturbances in the left lower quadrant of the abdomen. In a third group the characteristic symptoms and signs of diverticulitis were obvious, simulating a left-sided appendicitis, with leucocytosis. The figures of Starr Judd and Pollock, writing also last year (49), show how a competent modern X-ray examination has revealed the frequency of the condition. They report that in one-third of the positive X-ray examinations at the Mayo Clinic, in the last year, diverticulosis or diverticulitis was present. They discuss in detail the various surgical complications and their treatment, leaning to conservative treatment—'we are convinced that the process is not progressive, and that unless there are symptoms from the diverticula no treatment other than palliative, such as regulation of the bowel movements, is indicated'.

All writers are agreed that the diverticula are rare in the rectum. Although their orifices are sometimes seen with the sigmoidoscope (Gant (45), Yeomans (65), Masson (53), Gordon Watson (63)), Starr Judd and Pollock express the opinion, with which we agree, that that instrument is not as a rule of much use in detecting the condition. The diagnosis is more easily and accurately made by a barium meal or enema; and with all other diagnostic means the majority of cases are missed.

Incidence.

Diverticulosis of the large intestine was recognized in precisely 100 patients in 1,000 consecutive radiological examinations of the alimentary canal. These 1,000 examinations were made in those seeking relief for some abdominal disorder or, if not actually complaining of abdominal symptoms, undergoing an investigation with the object of finding a hidden cause for general ill health or for disorder in other parts of the body, such, for example, as the joints. The incidence of the condition in the general population would naturally be less. Nevertheless, as diverticulosis was present in 10 per cent. of those examined, it must be concluded that it is a common disease.

In the 100 cases, 29 were women and 71 men. It is not known why one sex should be more liable to the disease than the other. If constipation, as has been suggested, is a main cause, we should have expected the condition to be commoner in women than men.

The age of incidence is in the latter half of life. The average age of the 1,000 patients investigated was 45, whereas the average age of the 100 with diverticulosis was 58 years; the youngest of these patients was 35, the oldest 77.

As the recognition of the disease depends, with rare exceptions, upon

radiology, there are no data to determine whether *heredity* plays a part in its aetiology.

Morbid Anatomy.

A full description of the macro- and microscopical anatomy is given in the paper of Telling and Gruner with excellent illustrations. In this series there was no mortality, and our observations are based solely upon the clinical and radiological findings.

The *distribution* of the diverticula in the 100 cases was as follows:

Pelvic colon	58 cases
Descending colon	46 "
Iliac colon	16 "
Transverse colon	13 "
Ascending colon	10 "
Whole colon	8 "
Caecum	7 "
Appendix	5 "
Rectum	3 "

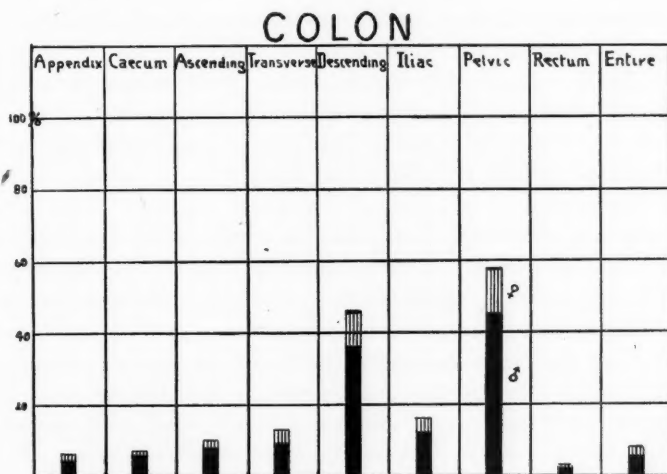


FIG. 28.

Fig. 28 expresses graphically the above figures and the sex incidence, the upper striped part of each column representing the females.

Method.

In all cases the buttermilk meal is used (p. 5) and observations are repeated until after the bowel is empty. When constipation is present, screening is continued up to ninety-six hours; after that an aperient is given, preferably the kind which the patient has been in the habit of using. We then learn, incidentally, whether his customary aperient does evacuate the bowel, which is by no means always the case. When the lumen of the gut is clear the residues

are observed daily for a time and afterwards at longer intervals; if, for example, a stercolith is to be watched, once a week. The bowel must be observed at all angles. When an area is under suspicion a series of films should be exposed during one breath.

Opaque material in previously unobserved diverticula may often be seen through a coating of barium in the bowel.

We have on several occasions recognized more residues after the meal than after a barium enema.

First Stage. The Prediverticular State.

This condition has been recognized and observed by one of us in the course of routine radiological work and was first referred to in a short note two years ago (52). No detailed description has hitherto been published. The appearance is characterized by a ragged outline of the wall of the bowel, which does not dilate even in the most favourable position. If one aspect only of the wall is involved the contraction is less. This appearance is not the result of irritation from the small herniae, but precedes their formation.

Pl. 6, Fig. 29 (♀, aged 55) shows a prediverticular state of the pelvic colon, the affected area being traced for comparison. The prediverticulous area does not show the normal segmentation of the bowel, which can, however, be seen plainly on the opposite (left-hand) profile of the same piece of bowel. Well-formed diverticula are seen near by.

The prediverticular state, like other fine details in the alimentary canal, is shown best, in our experience, with the buttermilk meal. If a starchy medium is chosen to suspend the opaque compound, such a piece of gut will usually be in a state of inhibition.

Such areas have been observed in twenty of our hundred cases of diverticulosis of the large intestine⁴ in positions varying from the caecum to the pelvic colon, most often in the latter. They are generally small and limited, but not always. We have seen all the colon involved in little patches. The largest continuous stretch over which the appearance has been seen is the whole descending colon and sigmoid. In sixteen of these cases small diverticula could be recognized in or close to the affected areas, and in several large diverticula existed in other parts of the bowel.

We think that the process which gives this radiographic appearance rarefies the wall in the first instance, and this is supported by the observation of L. B. Wilson, who stated that he found thinning of the circular muscle adjacent to diverticula.

It is while this stage of the disease is in progress that the minute herniae, which later constitute the necks of the diverticula, are pushed through.

In Pl. 7, Fig. 30 (♂, aged 61), the left-hand figure shows a stretch of the

⁴ The prediverticular state has been observed in 15 more patients since the completion of the 1,000 cases referred in this paper, i. e. 35 in all.

sigmoid flexure in the prediverticular state. The disease involves the whole circumference of one part of the bowel, with the result that a characteristic ring constriction is shown. Proximal to this the lower side only of the wall is involved, and the narrowing is therefore less.

Pl. 7, Fig. 31 (σ^7 , aged 30) is from another case in which the entire circumference of the bowel is involved over a longer stretch. Segmentation is almost lost, but can be made out at parts less completely affected.

If the disease in such a case involves the whole of the circumference of the bowel, an explanation is needed of why the diverticula at a later stage are commonly found in rows. The reason is probably the anatomical one that the small herniae which are present in the next stage of the disease penetrate most easily where the wall is weakest, namely, between the bands and at the entry of blood-vessels.

A local pericolic inflammation may simulate the X-ray appearance of the prediverticular state. Pl. 4, Fig. 32, for example, shows the transverse colon at a point where it was adherent to a jejunal ulcer, the shadow of barium in which can be seen close to the upper border of the bowel. An arrow points to the ulcer. The diagnosis was confirmed later at operation. The outline is nearly, but not quite, that of prediverticular disease. The differentiation lies in the asymmetric convex impressions, which are also broader, with less abrupt spines, altogether less neat than in diverticulosis.

Another appearance which may simulate the prediverticular state is that of a trail following a mass movement in an irritable colon. This is, of course, only temporary.

The outline of a prediverticular area is not unlike that of the barium-filled small intestine. Pl. 8, Fig. 33 (σ^7 , aged 56) illustrates this. There is diverticulosis of the descending and pelvic colon with the prediverticular state. A loop of jejunum shows in the upper part of the photograph.

Second Stage. The Developed Diverticula.

At a later stage of the prediverticular state, if a fairly large area is involved, and not small patches only, an irregular segmentation, broad and deeply serrated, with narrow haustra, may be observed. Some of the little pockets will probably now be visible. The serrated appearance is perhaps that referred to by Keith, who described contractions of the taenia throwing the colon into circular concertina-like folds. Pl. 7, Fig. 34 shows this well on the posterior border of the descending colon. The anterior (left) border shows the prediverticular state. This patient had returned for examination after having been treated seven years before, at the age of 48, for duodenal ulcer, with albuminuria. We had taken photographs of the bowel then and found no abnormality of the colon; and this has been confirmed by a careful re-examination of the plates.

Fig. 35, each part of which is made from tracings from films, shows diagrammatically the appearances to watch for as additions to ordinary regular

or irregular segmentation; it represents the various stages of development of the sacculi as well as the different ways in which they may fill.

No. 1 shows part of a transverse colon with a small protrusion; this is only one of a large number of all sizes that were present in this case. A year before many diverticula were seen in the descending colon, but none in the transverse colon, which then showed irregular segmentation.

No. 2 shows a similar condition slightly larger; the crescent shape of opaque material partly surrounding the inopaque residue is already present in two of the pockets.

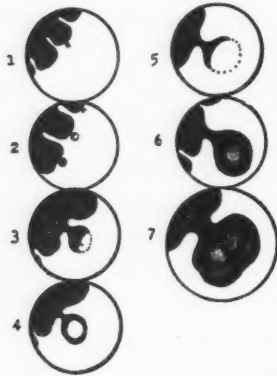


FIG. 35.

conspicuous after evacuation of the lumen of the bowel.

No. 6 shows a similar diverticulum, but with a wider mouth and more complete filling.

No. 7 shows a very large sacculus with a wide mouth.

All such shadows as these, additional to the haustra, are diverticula.

We have observed infant diverticula increase to a diameter of 5 mm. in one year. This patient, like some others in whom the largest diverticula have been found, had loose stools.

Pl. 7, Fig. 36 (♂, aged 69) shows such large diverticula. All of them except two emptied within twenty-four hours after evacuation of the opaque contents of the colon. It may be supposed that when the motions are fluid the pockets fill and empty easily and therefore undergo more often the dilatation which would accompany every fresh filling. It follows that there is less retention in big pockets and less risk of irritative putrefaction or of the formation of permanent residues or stercoliths.

Pl. 8, Fig. 37 (♂, aged 69) shows a variety of shapes and filling appearances, including the characteristic crescents. It could be seen on the negative that most of these pockets had narrow necks.

Residues in Developed Diverticula.

The smallest diverticula of the colon are not seen as residues, for they do not hold faeces for any length of time. It appears that the liability to retention

does not generally arise until after the little hernia has exceeded the depth of the outer peritoneal surface, that is, until the pocket has begun to spread beyond the neck. When retention is established, the width of the neck determines the rate of emptying of the pocket, subject no doubt to variation in the consistency of the bowel contents. The residues after the barium meal show the characteristic crescents, which are apt to be overlooked by even the most alert. The shadows are small, but are recognizable; and such pockets generally retain faeces longer than those which fill uniformly.

It is, therefore, after the evacuation of the opaque meal that we see best the approximate number of developed diverticula. It is because this observation has been neglected, and films have not been taken at that stage, that the frequency of diverticulosis has remained so long unrecognized. By observing and following up this stage we learn which diverticula material will readily leave and which contain permanent residues or stercoliths. In some cases it may be found that the majority of the pockets empty soon after the bowel contents, only one or more containing stercoliths.

Pl. 8, Fig. 38 (♂, aged 69), taken at 120 hours, one hour after the barium had left the lumen of the bowel, shows residues along the whole colon. Eighty hours later Fig. 39 was taken. It shows about 12 fewer diverticula; the larger ones have emptied, and in many the opaque contents have diminished. A trail of small specks can be seen in the distal part of the transverse colon. These are fragments of diverticular residues passing out. Eleven days later there were only a few residues and an opaque content in the appendix. Several other stercoliths could, however, be recognized on the negative.

We have seen opaque residues from a barium meal which had been given five months before the patient was admitted, observed, of course, before any fresh barium was given. A barium-coated stercolith could also be seen, and is shown by the arrow in Pl. 4, Fig. 26. The anterior view of the barium enema showed only a few diverticula. If reliance were placed upon such a photograph alone the real data would be lost.

In advanced cases accumulations in diverticula may assume large proportions. Pl. 8, Fig. 40 (♀, aged 63) shows the contents of a group of large diverticula in a patient with advanced diverticulitis. No barium had been administered.

*Third Stage. Inflammation and Thickening of the Wall of the Bowel.
Diverticulitis.*

The third phase of the disease has been recognized and well described by many authors, of whom may be mentioned in this country Moynihan, and Telling and Gruner. It is the stage of obvious abdominal symptoms. Such signs or symptoms may, however, arise at any stage of the disease, for inflammation may be confined to one diverticulum and very slight pains or sensations may justify the term diverticulitis.

The disease does not usually progress to this stage—that is to say, well-established diverticulitis is uncommon. It was present in its fully developed form in five of our hundred consecutive cases.

If the technique recommended for the giving and the observation of a barium enema is followed (52) the appearance of the bowel is unmistakable.

Pl. 8, Fig. 41 shows a narrowing of the bowel from diverticulitis, at the site of adhesion to the bladder.

Pl. 9, Fig. 42 (♂, aged 56) shows a typical area which has undergone inflammatory changes. The right-hand picture with its apple-like diverticula is the earlier one by eight months. On the left there is a change to a pear-like appearance, and the area involved has assumed a rigid aspect and would usually be felt through the abdominal wall provided it were within reach, though not in an obese individual, such as this patient was.

When the area involved is small and more ring-like the appearance is that of a row of slender spikes, parallel or at various angles, as shown in Fig. 43 (♂, aged 63). These are rigid, and contrast with opposite and adjacent haustra which are over-active in changing their shape. The lumen of the bowel may become occluded as the result of these hypertrophic changes, and subacute or acute obstruction result. This occurred in two cases out of the hundred, colostomy being performed in each.

Aetiology.

It is suggested that a reason why the sigmoid, and especially its lower outline, is the most commonly affected part of the bowel may be that it is especially exposed to bacterial damage. In observing the bowel in the X-ray room immediately before (Fig. 44) and after (Fig. 45) a good evacuation, it is clear that fluid or semi-fluid material is transported during or soon after evacuation to the lowest part of the sigmoid loop.

A comparison of these figures shows that the contents of the distal part of the transverse colon and the whole of the descending colon were passed, and that the opaque material lying in the sigmoid in Fig. 44 is that which formerly occupied the proximal part of the transverse colon. This semi-fluid material remains in the sigmoid loop, as shown diagrammatically in Fig. 46, gradually becoming less fluid and being added to during the following twenty-four hours. This would give a particularly favourable opportunity for toxic damage and bacterial invasion of the bowel wall.

The definitely localized appearance of areas of bowel in the prediverticular state indicates a local irritation in the early stage of the disease, and a bacterial cause is the first one that suggests itself. Such a cause would be more likely to be found if the secretion lying over the part affected could be investigated, particularly when an area at the prediverticular stage lay within reach of the sigmoidoscope. We have examined mucus obtained from such an area through the sigmoidoscope with negative results; but further and more thorough search is needed.

Whether or not it is possible or justifiable to collect material from the exact part involved, the examination of the dejecta might yield information.

Our colleagues, S. W. Patterson and J. G. S. Jeffery, have made bacterial examinations of the faeces in all the more recent cases; and attention was attracted by the frequency with which a haemolytic streptococcus was reported in cases of diverticulosis. Streptococci capable of causing haemolysis are, however, frequent in the faeces; they were present, for example, in thirty of the last hundred non-diverticulosis patients. In twenty-four patients with diverticulosis they were found ten times, which does not show much difference. In those, however, in whom the prediverticular stage was observed, at which any bacterial agency might be supposed to be most active, the incidence is greater, haemolytic streptococci being found in nine out of the last fourteen cases with pre-diverticular areas. It follows that of the ten diverticulosis patients in whom these streptococci were found, nine showed prediverticular areas.



FIG. 46.

Comparison with 100 patients of same average sex and age (58) but

without diverticulosis

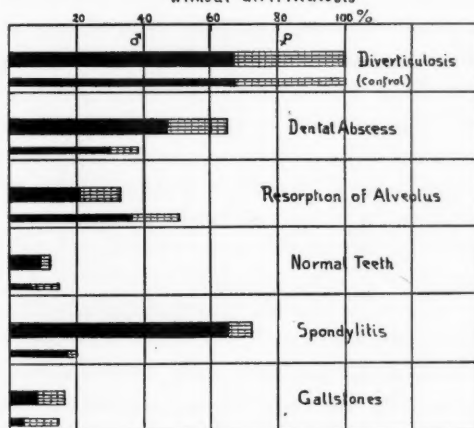


FIG. 47.

No conclusions can be drawn from these figures, but the possibility of an infective cause for diverticulosis led us to inquire into the association of the condition with other morbid states.

Association with other diseases. One of us (O. A. M.) first noted that *spondylitis* of the lumbar vertebrae was often found in the same patients as diverticulosis. Arthritic changes in the vertebrae are, of course, not infrequent in later life, but the following figures suggest that the association of the two conditions is not a coincidence. In 100 recent consecutive cases of diverticulosis examined with this point in view, spondylitis was present in 72, i. e. 72 per cent., whereas in 100 non-diverticulosis patients of the same average age as the diverticulosis ones, i. e. 58 years, spondylitis was present in 20 per cent. In 1,000 consecutive patients spondylitis was present in 19 per cent.

Of the 100 diverticulous patients, 65 were also the subjects of small abscesses or septic apical granulomata of the teeth. In the control 100 patients of the same average age, 38 showed tooth abscesses. In the last 50 patients with diverticulosis, gall-stones were present 9 times; in 100 patients of similar age but without diverticulosis the percentage incidence of gall-stones was about the same, stones being demonstrated in 14 and strongly suspected in 3 more.

In Fig. 47 these associations are set forth graphically.

Leucocytosis without other obvious cause than the diverticulous condition was present in 15 cases.

Of other concurrent morbid conditions the *appendix* was diseased or had been removed in 9 cases; in 16 others it was under suspicion or could not be shown radiologically to be healthy. Eight patients were suffering or had suffered from duodenal ulcer, and 2 from gastric ulcer. Arthritis was present in 6; a diseased antrum in 2; severe sciatica in 2; cystitis, fistula, and kidney disease in 1 each.

It is clear from this recital that it is uncommon to find a case of diverticulosis without association with a lesion of an infective nature.

It has been suggested that diverticulosis is a consequence of colitis. Of our 100 cases, 5 gave a history of colitis, and 4 were suffering from it on admission; 1 other had formerly had dysentery. These figures do not support the view, as the incidence of colitis is less than in the other 900 cases in the series. We have also examined repeatedly and carefully in the X-ray room the bowel of patients with chronic colitis without finding evidence of diverticulosis. Further, none of our recent prediverticular cases gave a history of colitis. The irritation may, of course, be designated a local colitis, but the diverticulous colon seems to be but little liable to the general form of that disease.

Just over half the patients with diverticulosis, namely 53, gave a clinical history of *constipation*; 14 stated that the bowels had always been regular, 6 had diarrhoea, and 3 alternate diarrhoea and constipation. The remainder did not mention especially the bowels, but many of them were constipated. From a radiological point of view, there was sluggishness of the bowels with a rate of passage of more than 72 hours in 57; a normal rate was found in 28, and a rapid passage in 15. We do not know what proportion of the general population would radiologically show constipation. But as compared with 100 control non-diverticulous fellow patients of the same average age, the subjects of diverticulosis were the less constipated.

Constipation probably favours diverticulosis, though we do not think it is the primary cause, for reasons above given. But once an area of weakening of the bowel wall is established any increase of pressure or stretching of the wall would favour the formation or distension of the little herniae. The increase of pressure for this purpose must be from within the bowel, as from vigorous contraction of its muscular wall or distension with faeces or gas. The general increase of intra-abdominal pressure during straining would fall equally upon the peritoneal surface of the bowels and would protect rather than cause the small extrusions.

In six cases in the series *malignant growth* was present, in five of them in the alimentary canal. This incidence is about half that in our hospital population of the same average age. Cancer is not, therefore, a common association, though it may be noted that it was as frequent in this series as was the third stage of surgical diverticulitis.

Discussion. The association of diverticulosis with spondylitis and abscesses of the teeth appears to be more frequent than is explained by the age of the patients. That spondylitis and diverticulosis occur together might be explained on the view that they are both due to infective or both due to degenerative processes. The association of diverticulosis with apical tooth abscesses favours the infective view, and this receives support, we think, from the study of the prediverticular areas themselves. The irritative aspect, the tenderness sometimes observed when pressing gently on an affected loop of bowel on the X-ray table, and the improvement in the appearance, and the lessened spasm, following gentle lavage of such a loop (see Pl. 7, Fig. 30, and p. 30), all favour an inflammatory irritative process rather than a passive degeneration, without surrounding reaction, such as would be comparable to the gradual formation of a patch of atheroma in an artery.

Whatever the process, the result is a weakening of the bowel wall so that minute extrusions pass through between the muscle fibres. Such extrusions would naturally be more likely to occur where some anatomical weakness pre-existed, such as at places where the blood-vessels pierce the outer layers of the gut.

When the herniating process was once begun, fluid faeces or gas would pass more easily into the pockets and distend them farther than would hard inspissated material. It is suggested above that the sigmoid loop is a part of the bowel where semi-fluid contents probably remain stationary a longer time than in other parts of the colon, probably even more than in the caecum, the contents of which are disturbed frequently by additions from the small intestine. In the constipated it might be expected that the sigmoid would be occupied as a rule by harder faeces than in others, but this would only be so if aperients were not taken. Most constipated people, however, are taking aperients regularly. In this series, for instance, our colleague, R. S. Allison, found that, of the 51 patients who complained of constipation, 44 stated that aperients were taken. The drugs used were as follows: salts, 10 cases; cascara, 8; patent pills or purgatives, 6; aloes, 4; castor oil, liquorice, senna, 1 each, that is 3; paraffin, 8; enemas and douches, 5. If we omit the paraffin, enemas, and douches, it is seen that 31 of the 51 were taking regularly irritative aperients such as would produce loose stools. Seven other of the patients, who did not complain of constipation, took salts regularly. A history of constipation, then, may frequently imply that the sigmoid is likely to be a depot for fluid faeces rather more often than in normal folk.

Symptoms.

Of the twenty cases in our series in which the prediverticular state was observed, in eleven it was closely associated with the presence of formed diverticula, with or without diverticulitis. These cases are not, therefore, of value in deciding whether or not any symptoms may accompany the earliest irritative stage of the disease. Of the remaining nine, one had no symptoms, six complained of constipation, and two of diarrhoea. Radiologically, every one of these patients was constipated, including those who complained of diarrhoea; that is, in each the time of passage of the barium meal was longer than normal. One had much flatulence and two lumbago.

In two of these patients the prediverticular area was tender to palpation on the X-ray table.

The second stage of diverticulosis, when the pockets are fully formed, may last for years. In many cases there is no X-ray evidence of irritation and no symptoms. In others there may be flatulence, with discomfort or pain, dull or colicky, over the affected bowel, constipation, or irritative diarrhoea; and the signs and symptoms merge gradually into the third stage, that of diverticulitis, when some degree, even if only slight, of inflammation, with resulting thickening or adhesion, has become established. Great care is necessary in drawing conclusions, because, as above mentioned, nearly all cases of diverticulosis are associated with some infective condition in another part of the body which may give rise to symptoms of its own. The most frequent association, however, is the triple one of diverticulosis, spondylitis, and abscesses at the roots of the teeth.

The following are two typical accounts: A man of 51, who had frequently had influenza, complained of repeated lumbago, headaches, passage of much flatus by the bowel, and constipation. The teeth were defective: X-rays showed abscesses at the apices of some of them, also exostoses in the region of the fifth lumbar vertebra, and a prediverticular state of the descending and pelvic colon.

A man of 57 had noticed for four years a sense of incomplete evacuation of the rectum. His abdomen had been opened twice in that time, and the appendix removed, but no adequate reason for his discomfort found. The sigmoid had been stitched to the anterior abdominal wall. On admission he complained of constant discomfort in the left iliac fossa, a sense of incomplete evacuation, and frequent micturition after an action of the bowels. X-ray examination showed diverticulosis of the descending colon and the sigmoid with mild diverticulitis. With treatment the general health improved steadily and the symptoms diminished. On readmission eighteen months later for another condition, no complaint was made of the abdominal symptoms, which had gradually disappeared.

The features of the third stage of established diverticulitis are pain, intermittent and subacute, usually in the left iliac fossa, and a tender tumour. The

walls of the diverticula have become infected, with resulting inflammation extending to the outer coats of the bowel, the peritoneum, and adjacent organs. Even at this stage the tendency is to chronicity or very slow progress.

We will now consider the symptoms in the 100 cases, taking all stages together, bearing in mind that in only five was there advanced or surgical diverticulitis with gross inflammation and tumour, with or without obstruction. In the following summary, symptoms definitely associated with, or explained by, other lesions are not included.

In 29 out of the 100 patients with diverticulosis no symptoms were referable to the condition. In the remaining 71, if we exclude constipation only, with perhaps a little flatulence, there were 45 patients in whom the symptoms complained of were judged to be referable to, or associated with, the diverticulosis.

The following is a summary of the symptoms, including constipation, in the 71 patients :

Constipation	58 times
Flatulence	22 "
Abdominal pain	21 "
Abdominal discomfort, distension, or indigestion	21 "
Pain or discomfort before or after defaecation	6 "
Diarrhoea	6 "
Irregular micturition	4 "
Alternating constipation and diarrhoea	3 "

Other symptoms mentioned were headache, malaise, nausea. Blood in the stools was met with only once.

The pain or discomfort was generally below the navel and most often on the left side.

To summarize this section: In about a third of 100 subjects of diverticulosis there were no symptoms referable to the condition, and in a number of others no symptom except constipation. In nearly a half flatulence and abdominal pain or discomfort were frequent.

The *diagnosis* is made by radiological examination. There is no other means by which the condition can be recognized with certainty or its extent assessed, excepting by the revelation of advanced diverticulitis or pericolicitis at an operation for an inflammatory tumour or for obstruction.

The *prognosis* with adequate treatment is good. In thirty-six out of the fifty-three patients who complained of symptoms, including a few in which the main symptom was constipation, complete relief was obtained after a few weeks' treatment. Five others lost all symptoms except occasional flatulence, and in others there was improvement. There was no death in this series. Our experience is contrary to the pessimistic view of some writers on this subject, who express no hope of relieving the patient whose symptoms are due to multiple diverticula of the bowel. Such views probably arise in the first place from a contemplation of the morbid anatomy of the disease without a serious attempt to treat the patient; or, secondly, from the archaic view still prevalent that medical treat-

ment for any disease which has not yet disabled the patient has its basis in a prescription, and can be carried out adequately amid the occupations and distractions of the office and the home.

Treatment is directed to the bowel and to the general condition of the patient. The mouth is cleansed, teeth with abscesses at the roots are removed, and any other sources of infection, such as an inflamed appendix or gall-bladder, dealt with as far as possible. Paraffin is given in all cases, including those with diarrhoea, with the object of lubricating the lining of the bowel, including that of the little pockets, and preventing long delay of faecal matter therein, thus lessening the risk of putrefaction and inflammation. When all symptoms are gone the patient with diverticulosis is still advised to take paraffin for the rest of his life, reducing the dose to a teaspoonful night and morning if the bowels are loose. He is instructed not to strain at stool, but to take time, making a short effort every third breath.

An intestinal douche of normal saline solution is given on alternate days. It is naturally important, with so many weak spots in the intestinal wall, that the fluid should be run in at a low pressure, the receiver being raised not more than 18 inches above the rectal tube. The patient lies on the left side, taking deep breaths till $1\frac{1}{2}$ to 2 pints has entered, then turns gently to the right side, taking half a dozen deep breaths in that position. With this procedure the whole of the colon can be easily filled, as we prove every day with the barium enema in the X-ray room. In an irritative state of the bowel intestinal douching is sometimes followed by temporary increase of discomfort, with benefit later.

Improvement to the prediverticular state can be recognized radiologically after such treatment, as in the left-hand picture of Pl. 7, Fig. 30, which shows a prediverticular ring constriction. In the right-hand picture, after treatment, the constriction is not obvious.

The bowels are further aided by a lacto-vegetarian (anti-constipation) diet, containing plenty of fruit and greens; for example:

- 7 a.m. $\frac{1}{2}$ oz. of paraffin in 2 oz. of warm milk.
- 8 a.m. Coffee and milk; one tablespoonful of milk sugar; wholemeal bread; butter; honey or marmalade.
- 10.30 a.m. A glass of buttermilk; wholemeal bread and butter.
- 1 p.m. Fish (cooked any way); butter sauce; salad and dressing; compote of fruit; cream; toast and butter.
- 4 p.m. Coffee, with milk or cream; marmalade; wholemeal bread (toasted if desired) and butter.
- 7.30 p.m. Vegetable soup; some egg dish (poached, scrambled, or omelette) with vegetables or fruit; for instance, may have jam or jelly omelette or omelette aux fines herbes; cream cheese; wholemeal bread; butter.

Such a diet is of course modified to suit the individual.

The general tone is raised by prescribed rests and exercise, by massage to

the muscles and, in some cases, to unaffected parts of the abdomen; generally, however, the abdomen is avoided, and a diverticulous area is never massaged.

Such symptoms as flatulent indigestion and lack of appetite are treated by carminatives or tonics, and any other medicines which seem to be called for are given.

In advanced cases, which are rare, if obstruction or other surgical complications arise, suitable operative measures must be taken.

The removal of a diverticulous area of bowel has been recommended. If there is pericolitis with infection of the bowel wall and adhesions, this is surgically often neither possible nor safe. If there is not pericolitis the favourable course of the disease does not justify such an operation. Further, in a few cases, we have observed the spread of the condition in successive years in widely different areas of bowel, and there is no evidence that removing one part would prevent diverticulosis from arising in the remainder.

With attention to the hygiene of the bowel and the body generally, as detailed above, the large majority of the patients who complain of symptoms arising from multiple diverticula of the colon will have their discomforts allayed and complications warded off. Even in advanced diverticulitis, after colostomy had been performed, regular attention to the cleansing of the bowel has, we are informed by Sir Berkeley Moynihan, allowed of such a degree of recovery that it has been possible to close the opening.

Our experience in the past seven years makes it probable that if diverticulosis is adequately recognized and treated the proportion of cases that progress to diverticulitis will be small.

Summary.

Diverticula of the duodenum are not uncommon. They were observed with the X-rays in 38 patients out of 1,000 consecutive radiological examinations.

Twenty of the patients were women and 18 men. The youngest patient was 21, the eldest 75, the average age being 55 years. The largest pouch measured $4\frac{1}{2}$ inches in vertical diameter; the average size was about that of a walnut.

In two patients who were re-examined after four and seven years respectively, the development of a pouch from a small to a considerable size was observed.

In 18 of the 38 cases the symptoms for which the patient sought relief were thought to be due to irritation from the pouch or pouches. An analysis of the symptoms is given, and an account of some typical cases.

In 13 out of the 18 patients complete relief was obtained by treatment directed to aiding the pouch to empty, to lubricating and disinfecting its contents, and to correcting or relieving any associated symptoms. In one case of multiple duodenal and jejunal pouches, gastro-enterostomy was performed with success.

In the same series, *diverticula of the jejunum* were observed in 7 patients, of the *ileum* in 7, and of the *appendix* in 6 patients.

Diverticulosis of the large intestine is frequent, having been observed in 100 out of 1,000 consecutive cases. The diverticula are small and multiple, may be found in any part of the colon, but are commonest in the pelvic colon.

Of the 100 cases, 29 were women and 71 men; the youngest patient was 35, the eldest 77, the average age 58 years.

A prediverticular state can be recognized radiologically, characterized by fixity of the affected part of the bowel wall, with small irregularities. This is the first stage of the disease, at which the minute herniae begin to develop. The second stage of diverticulosis is one of formed diverticula. The third stage of diverticulosis is called diverticulitis. Inflammation has now spread from the pouches to the walls of the bowel and surrounding parts. This stage was well developed in 5 only of the 100 cases.

It is suggested that diverticulosis is the result either of a degenerative or of an inflammatory process. Its association with spondylitis of the lumbar spine, which was found in 70 per cent. of the diverticular patients as compared with 20 per cent. in a control series, might favour either view; but the inflammatory appearances of the prediverticular state and the association, nearly as frequent as that of spondylitis, with abscesses at the apices of the teeth, also with other septic conditions in various parts of the body, favour an infective origin. The demonstration of the prediverticular state particularly, which has now been observed in 35 patients, makes it improbable that diverticulosis is due to mere passive extrusions in a weak but otherwise healthy gut. An explanation is offered for the greater frequency of diverticulosis in the loop of the pelvic colon.

An account is given of the radiological appearances of formed diverticula and of the characteristic appearance seen in the third stage of established diverticulitis.

Forty-five of the 100 patients complained of symptoms attributable to the diverticula.

The condition is amenable to treatment, which is directed to the lubrication, cleanliness, and proper action of the bowel, and the health of the body generally.

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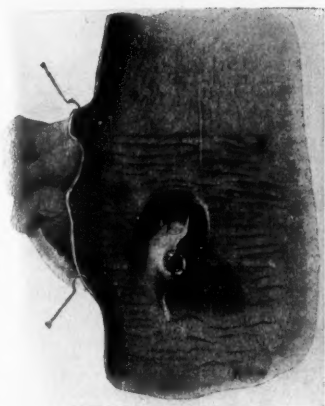


FIG. 1



FIG. 2

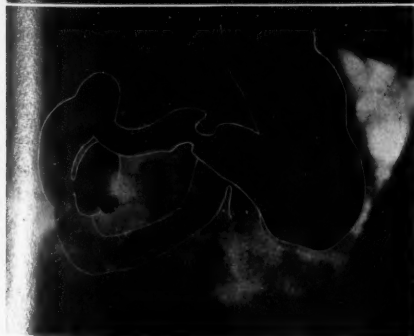
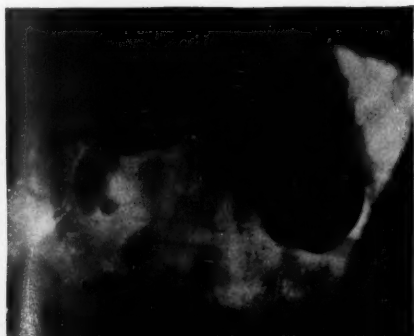


FIG. 4

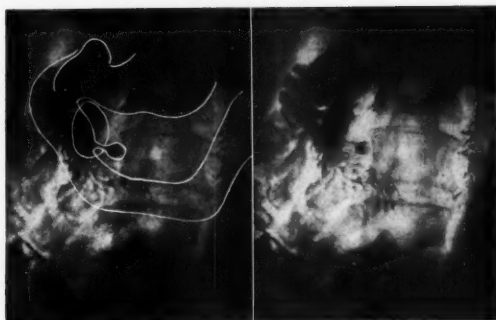


FIG. 5

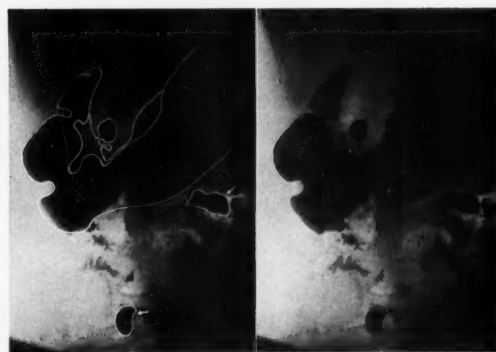


FIG. 6



FIG. 7



FIG. 9



FIG. 10



FIG. 13



FIG. 11



FIG. 12

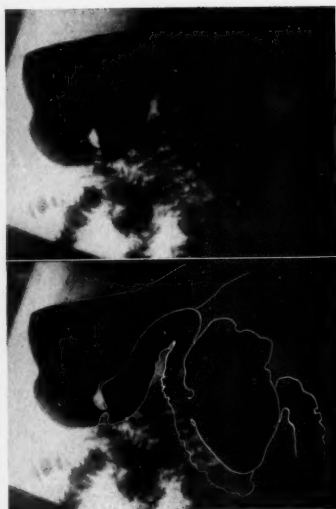


FIG. 14



FIG. 15

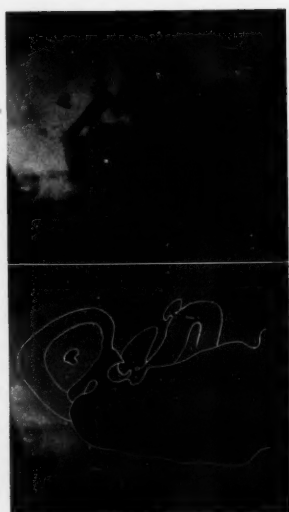


FIG. 16



FIG. 18



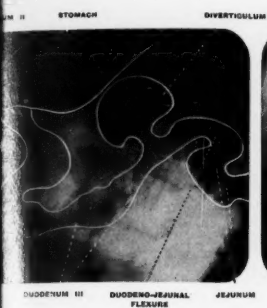


FIG. 17

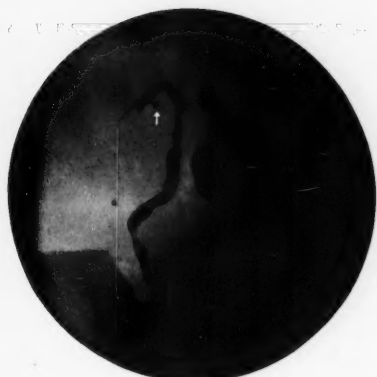


FIG. 20

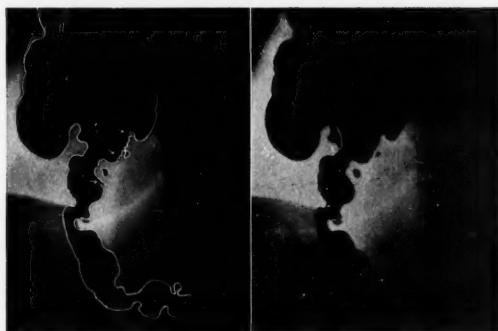


FIG. 19



FIG. 26

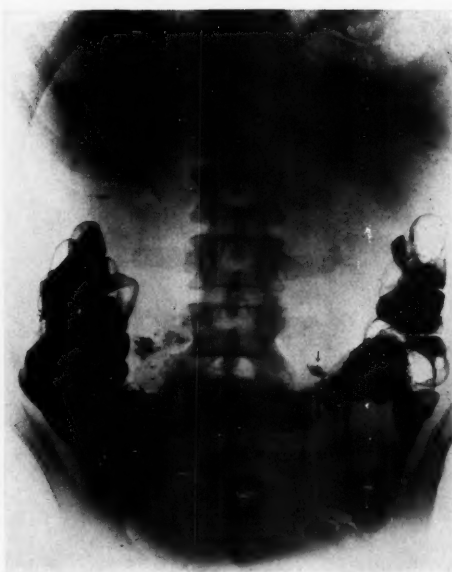


FIG. 32

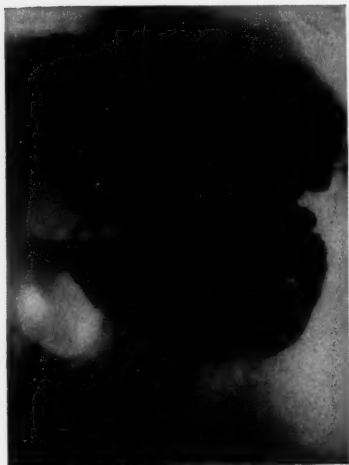


FIG. 22



FIG. 23



FIG. 24

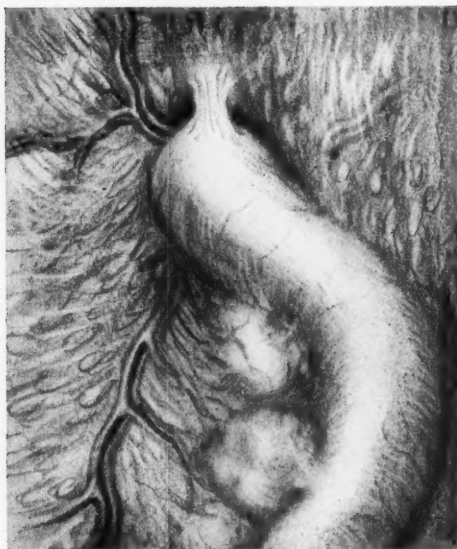


FIG. 25



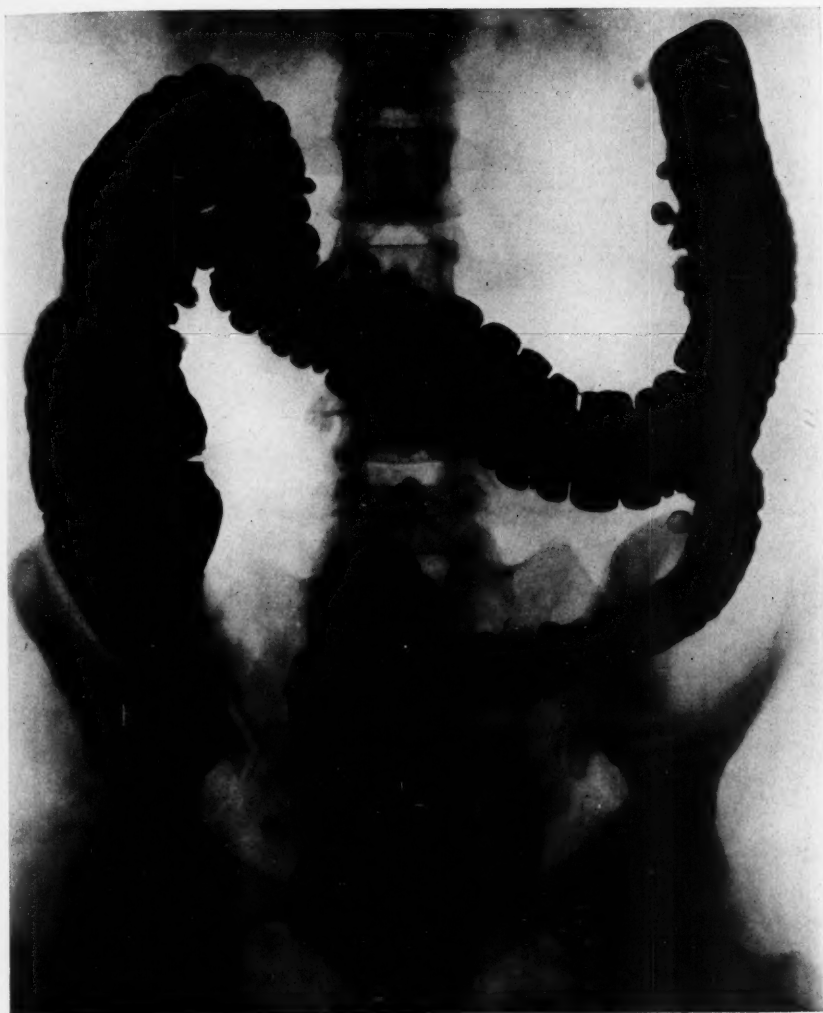


FIG. 27

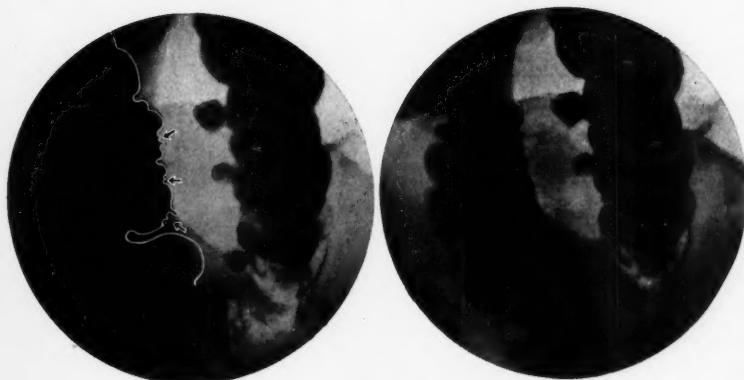


FIG. 29

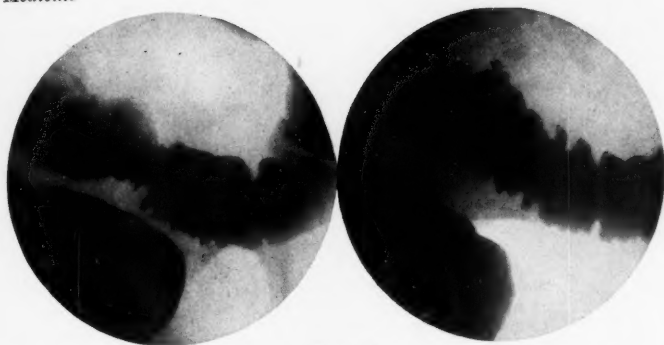


FIG. 30



FIG. 31



FIG. 34



FIG. 36



FIG. 37



FIG. 38



FIG. 39



FIG. 41

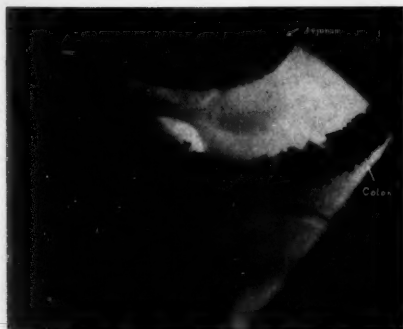


FIG. 33

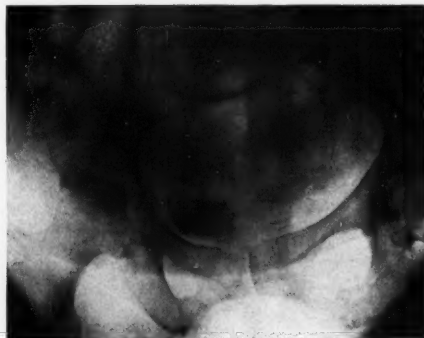


FIG. 40



FIG. 42



FIG. 43



FIG. 44



FIG. 45



THE RELATIVE PREVALENCE OF SO-CALLED ENDO-
CARDITIS LENTA BEFORE AND AFTER THE WAR:
A SURVEY OF 195 CASES¹

By GLADYS M. WAUCHOPE

ENDOCARDITIS LENTA was the name given by Schottmüller (1) in 1910 to five cases of subacute infective endocarditis in which the infecting organism was the *Streptococcus mitior seu viridans*, an organism which he had isolated and described in 1903 (2).

In later literature the name 'endocarditis lenta' has often been used as synonymous with 'subacute infective endocarditis' and 'subacute bacterial or bacteriaemic endocarditis' to denote the more chronic forms of infective endocarditis, irrespective of the nature of the infecting organism. It is used in this sense in the present paper, cases of rheumatism being excluded.

It is generally agreed that endocarditis lenta has become more common in recent years. Curschmann (3) gives the following figures of the mortality at the Medizinische Klinik zu Rostock:

1900-1905	1906-1910	1911-1915	1916-1917	1918	1919	1920	1921
7	9	9	3 2	3	3	4	12
15							

It is supposed that this increase is in some way due to the war, the Germans going so far as to call the disease 'Kriegs-Endocarditis' (4), while recent writers in England, e.g. Coombs (5) and Starling (6), have noted that it affects strong healthy males, a large proportion of whom served in the army. It has also been observed that the type of disease as it occurs in ex-soldiers is more chronic than that described by Schottmüller (1), or by Osler (7) and Horder (8) writing at the same date in this country. These conclusions have been tested by tracing the incidence of the disease at the London Hospital from the beginning of 1907 to the end of 1924. The series comprises the cases which came to autopsy during those years (125 cases), and, in addition, the cases admitted in the years 1911 to 1923 on which no autopsy was performed, making 195 in all. The period covers years before, during, and after the war; the patients all came from approximately the same district, and include ex-soldiers and civilians; the only apparent new factor in the environment arose when men went into the army, so that it is

¹ Received June 8, 1925.

possible to trace the influence of the war on the incidence of the disease. Further, the number of cases is comparatively large, and the average number of medical in-patients in thirteen of the years under consideration was 8,342 per annum, figures great enough to make statistics drawn from them fairly reliable.

The following signs and symptoms have been taken as diagnostic in conjunction with a cardiac valvular lesion and irregular or remittent pyrexia, viz. finger clubbing, Osler's nodes, purpura, splenic enlargement, anaemia, embolic phenomena, albuminuria, and haematuria. In 125 cases the diagnosis was confirmed by autopsy. In 37 of the remaining 70, a positive blood-culture was associated with typical signs and symptoms; in the remainder, two at least of the cardinal signs and symptoms were present, together with a typical temperature and cardiac lesion, and in 28 a diastolic murmur was heard at the aortic area.²

A certain number of probable cases, in which the evidence of the notes is doubtful or insufficient for a certain diagnosis, have been excluded.

In reviewing the cases, it has been found impossible, either on clinical or pathological grounds, to draw clean-cut lines between the acute, subacute, and chronic forms of infective endocarditis; the cases have, therefore, been divided arbitrarily on a time basis as follows:

I. All cases of infective endocarditis with a history of less than three months' duration have been considered as acute infective endocarditis, unless there was definite post-mortem evidence (e. g. organization of the vegetations on the valves, scarred infarcts, chronic inflammatory spleen) to show that they were of the subacute or chronic type. The notes of over 280 such cases have been examined and excluded altogether from the statistics.

II. Cases of over three months' duration from the first recorded symptoms of the disease have been regarded as cases of endocarditis lenta, and are the cases of which this paper treats. They have been subdivided for convenience under the headings 'subacute' and 'chronic infective endocarditis' as follows:

Cases in which symptoms were observed for between three and six months have been classed as subacute, together with cases which post-mortem evidence showed to belong to this class, although the recorded duration of the illness was less. A few which, on the clinical history, would have been classed here have been transferred to the chronic division on post-mortem evidence. There are 107 cases in this class.

² The following case has been admitted although only one of the cardinal signs was present, viz. an enlarged spleen.

A man, aged 52 years, had a febrile illness diagnosed as influenza seven months before his death. His temperature did not remain normal for more than a few days at a time after this attack. He had had rheumatic fever and syphilis in youth. When admitted to hospital one month before death, he was pale and wasted. The heart was enlarged, the apex beat being one inch external to the nipple line. There was a loud mitral systolic murmur. The spleen was palpable and reached two fingers' breadth below the costal margin. The temperature while the patient was in hospital was very irregular, rising to 103° F., and he had several rigors. A blood-culture was not made.

ENDOCARDITIS LENTA BEFORE AND AFTER THE WAR 37

Cases lasting for six months or longer from the onset of symptoms have been classed as chronic infective endocarditis, together with those of less observed duration, in which autopsy revealed calcification of the vegetations on the cardiac valves (88 cases).

The incidence of the disease, traced through a period of 18 years, is shown graphically in the following charts. The increase in the number of cases after the war is demonstrated in the first two charts.³ Chart I shows the fluctuation in the numbers of cases of endocarditis lenta which came to autopsy from January 1907 to the end of 1924 (125 cases). The number per 1,000 autopsies on deaths from all causes is indicated.

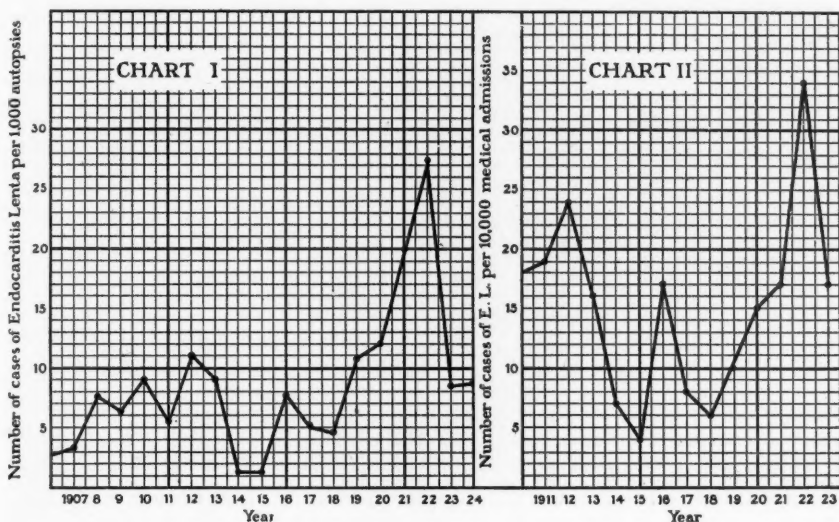
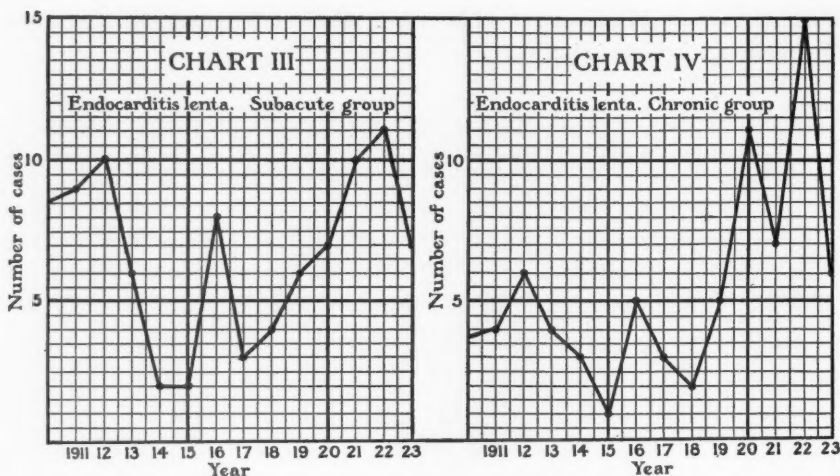


Chart II shows the number of cases admitted per 10,000 admissions to the medical wards from 1911 to 1923 inclusive (157 cases). A good many of those which did not come to autopsy have had to be discarded, the evidence being insufficient for a definitive diagnosis; the chart, therefore, probably shows less than the real incidence. However, as it confirms in broad outline the part of Chart I with which it coincides, the two together may be taken as showing a true tendency. It is evident that there has been a remarkable increase in the frequency of the disease, culminating in 1922. The curve would probably rise more gradually and start earlier but that the soldiers who developed symptoms before their discharge from the army were treated in military hospitals. It is noteworthy that the abrupt fall in numbers in 1923, shown in both charts, appears from Chart I to have continued in 1924, the curve of incidence of the disease reverting to the pre-war type.

³ Tables on which Charts I-X are based will be found on pp. 42, 43.

Charts III and IV demonstrate that the increase in numbers is due chiefly to cases of the chronic type. Chart III shows the fluctuation in the subacute class in which the increase of 1922 hardly exceeds that of 1912. Chart IV shows the incidence of the chronic form of the disease. Whereas the maximum number of cases in any year before 1919 was 6, the numbers rose gradually after 1919 to reach 15 in 1922, and fell in 1923 to 6 cases.

The actual number of cases is indicated.



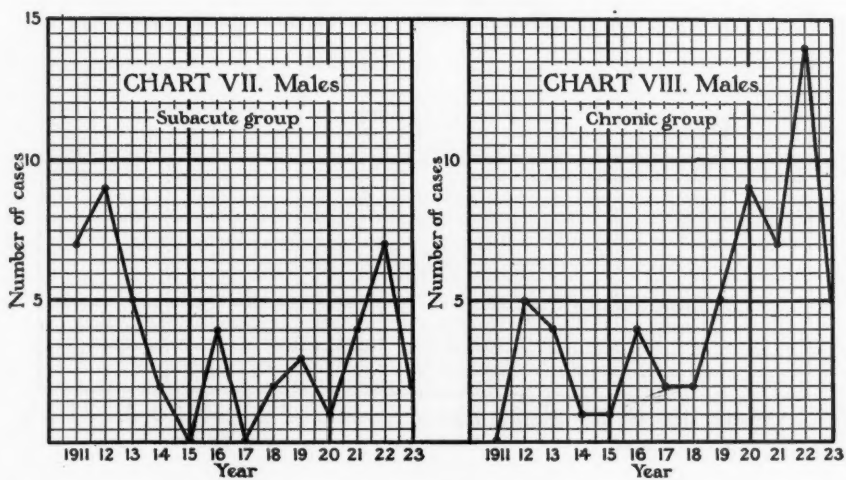
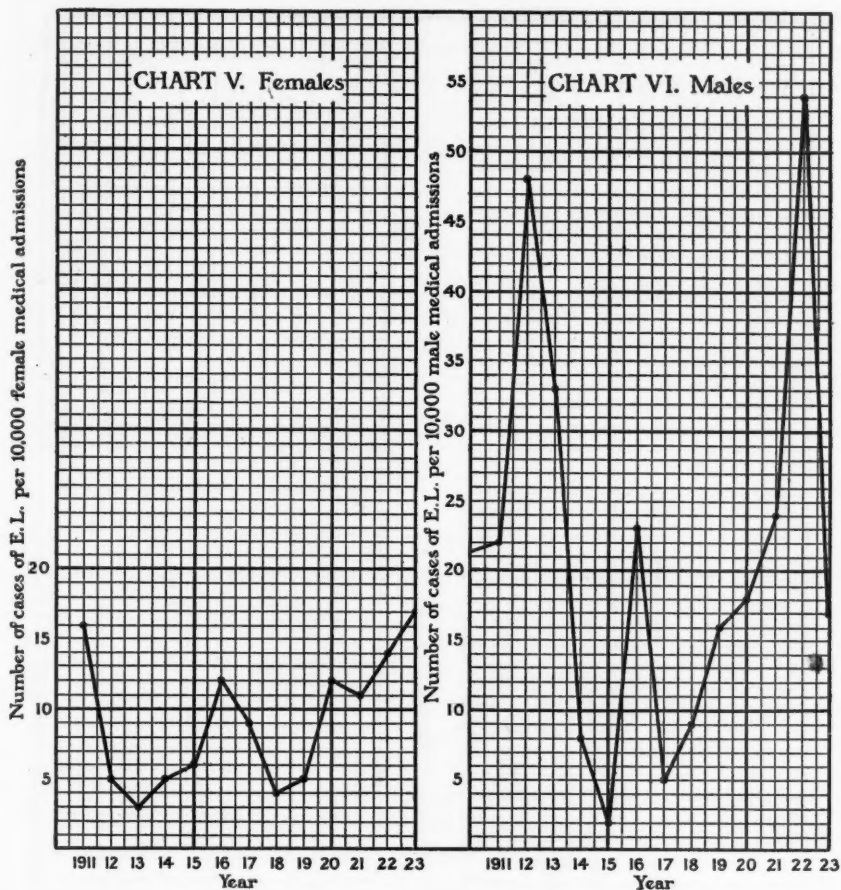
Sex Incidence.

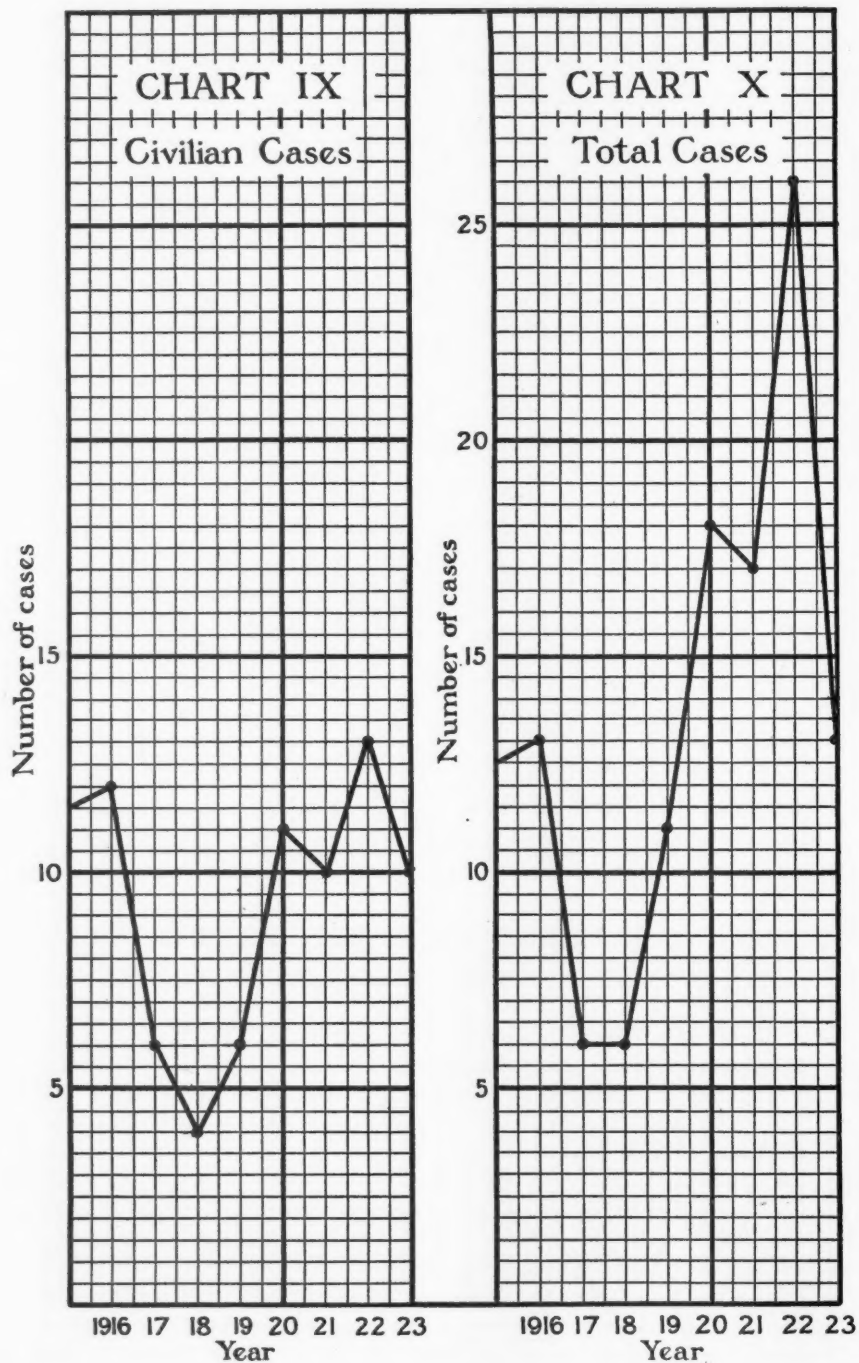
Charts V to VIII show that the rise was chiefly in males. The curve of incidence of endocarditis lenta in females (Chart V) follows an approximately even line, while that of males (Chart VI) is much more irregular, the greatest rise being in 1922. The number per 10,000 male medical admissions is indicated, and similarly for females. The actual numbers in Chart VI were 14 in 1912 and 21 in 1922.

It is clear from Charts VII and VIII that the rise of 1912 in males was due to cases of the subacute group, while that of 1922 was due to cases of the chronic group. The actual numbers are given in these charts.

Army Service.

Thirty-nine of the London Hospital patients suffering from endocarditis lenta were in the Services during the war; of these, 33 were in the chronic group and 6 in the subacute group. This proportion is the more remarkable since the total number of subacute cases exceeds that of chronic cases, being 107 and 88 respectively.





1916 was the first year in which an ex-soldier suffering from the disease was admitted. This man had trained for one year at home only. No cases in soldiers were admitted in 1917; thereafter the numbers gradually increased to 13 in 1922. The figures were:

$\frac{1918}{2}$	$\frac{1919}{5}$	$\frac{1920}{7}$	$\frac{1921}{7}$	$\frac{1922}{13}$	$\frac{1923}{3}$	$\frac{1924^4}{1}$
------------------	------------------	------------------	------------------	-------------------	------------------	--------------------

Charts IX and X show that there was no increase in the number of civilians suffering from endocarditis lenta corresponding to the increased incidence in cases viewed as a whole. Chart IX shows the incidence of civilian cases admitted to the hospital, and Chart X the total number of cases admitted. It is clear that the curve of incidence in civilians is not altered, and that the wave which culminated in 1922 advanced and declined *pari passu* with the admission of ex-soldiers.

The actual number of cases is shown in the charts.

Conclusions.

This series of cases supports the view already put forward and demonstrated by others that the disease known as endocarditis lenta became much more common after the recent war; that service in the army predisposed in some way to the acquirement of the disease, and that in ex-soldiers it tended to be more chronic in type than in civilians and women, in whom both the incidence and the form of the disease remained unaffected by the war.

My thanks are due to the Physicians of the London Hospital for permission to use the notes of their cases, and to Professor H. M. Turnbull for permission to use the records of the Pathological Institute of the London Hospital.

I wish also to thank Professor Turnbull for many valuable suggestions, and Dr. Robert Hutchison for repeated advice and help.

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⁴ Figures for 1922 are only available for cases which came to autopsy.

Number of Cases per Annum which came to Autopsy shown in Chart I.

Year.	Total Number of Autopsies.	Number with Endocarditis lenta.	Percentage.
1907	1183	4	0.34
1908	1285	10	0.78
1909	1288	8	0.62
1910	1208	11	0.91
1911	1265	7	0.55
1912	905	10	1.10
1913	885	8	0.9
1914	787	1	0.13
1915	719	1	0.14
1916	653	5	0.77
1917	581	3	0.52
1918	615	3	0.49
1919	645	7	1.09
1920	750	9	1.2
1921	598	12	2.01
1922	589	16	2.72
1923	604	5	0.83
1924	578	5	0.87
		125	

After 1911 necropsies were performed only on selected cases.

CHARTS II and X. *Admissions of Cases of Endocarditis lenta.*

Year.	Total Admissions into Medical Wards.	Number with Endocarditis lenta.	Percentage.
1911	6794	13	0.19
1912	6591	16	0.24
1913	6382	10	0.16
1914	7345	5	0.07
1915	7486	3	0.04
1916	7807	13	0.17
1917	7905	6	0.08
1918	9628	6	0.06
1919	11112	11	0.1
1920	12155	18	0.15
1921	9871	17	0.17
1922	7600	26	0.34
1923	7773	13	0.17
		157	

CHARTS III, IV, VII, and VIII. *Table showing Incidence per Annum of Subacute and Chronic Forms of Endocarditis lenta.*

Year.	Subacute.			Chronic.		
	Males.	Females.	Total.	Males.	Females.	Total.
1911	7	2	9	0	4	4
1912	9	1	10	5	1	6
1913	5	1	6	4	0	4
1914	2	0	2	1	2	3
1915	0	2	2	1	0	1
1916	4	4	8	4	1	5
1917	0	3	3	2	1	3
1918	2	2	4	2	0	2
1919	3	3	6	5	0	5
1920	1	6	7	9	2	11
1921	4	6	10	7	0	7
1922	7	4	11	14	1	15
1923	2	5	7	5	1	6
	<hr/> 46	<hr/> 39	<hr/> 85	<hr/> 59	<hr/> 13	<hr/> 72

ENDOCARDITIS LENTA BEFORE AND AFTER THE WAR 43

CHART V. *Cases admitted to Female Wards from 1911 to 1923.*

Year.	Number of Medical Females.	Number with Endocarditis lenta.	Percentage.
1911	3652	6	0.16
1912	3673	2	0.05
1913	3680	1	0.03
1914	3641	2	0.055
1915	3362	2	0.06
1916	4301	5	0.12
1917	4207	4	0.095
1918	5139	2	0.04
1919	6219	3	0.05
1920	6507	8	0.12
1921	5230	6	0.11
1922	3703	5	0.14
1923	3590	6	0.17
		52	

CHART VI. *Cases admitted to Male Wards from 1911 to 1923.*

Year.	Number of Medical Males.	Number with Endocarditis lenta.	Percentage.
1911	3142	7	0.22
1912	2918	14	0.48
1913	2702	9	0.33
1914	3704	3	0.08
1915	4124	1	0.02
1916	3506	8	0.23
1917	3698	2	0.05
1918	4489	4	0.09
1919	4893	8	0.16
1920	5648	10	0.18
1921	4641	11	0.24
1922	3897	21	0.54
1923	4183	7	0.17
		105	

CHART IX. *Cases in Civilians and Ex-soldiers, 1916-24 inclusive.*

Year.	Civilians.			Ex-soldiers.		
	Subacute.	Chronic.	Total.	Subacute.	Chronic.	Total.
1916	8	4	12	0	1	1
1917	3	3	6	0	0	0
1918	3	1	4	1	1	2
1919	4	2	6	2	3	5
1920	7	4	11	0	7	7
1921	9	1	10	1	6	7
1922	9	4	13	2	11	13
1923	7	3	10	0	3	3
1924*	2	2	4	0	1	1
	<hr/> 52	<hr/> 24	<hr/> 76	<hr/> 6	<hr/> 33	<hr/> 39

* Cases that came to autopsy only.

THE CLINICAL SYNDROME OF THROMBOSIS OF THE CORONARY ARTERIES¹

By J. W. McNEE

(From the Department of Medicine, Johns Hopkins Hospital, Baltimore)

With Plates 10 and 11.

Introduction.

IN sudden thrombosis of large branches of the coronary arteries there may occur a very characteristic clinical syndrome which has attracted little attention in Britain, and which receives scant notice in the text-books. The main features of this syndrome were noted in isolated instances long ago, but in the United States of America quite an extensive literature has grown up in recent years. It is impossible to say with certainty whether the condition is commoner there than in Britain, but by inference this would seem likely, since the clinical picture is so characteristic that it could scarcely be missed.

Embolism and thrombosis of large branches of the coronary arteries are everywhere recognized as causes of sudden death from cardiac infarction, but what requires emphasis is that, in the case of thrombosis at least, an immediate fatal issue does not always occur. On the contrary, patients who have presented all the symptoms and signs of thrombosis of a large branch may survive for years. It seems very necessary, therefore, to be able to recognize the clinical picture diagnostic of this serious cardiac disease.

In reading through some well-known accounts of angina pectoris in British literature, such as Clifford Allbutt's book, it is difficult to sift out the clinical accounts which probably refer to the special group of cases described here. It seems certain, however, that the condition referred to clinically as 'status anginosus' must frequently have been the result of a sudden coronary thrombosis.

The present paper is founded on three cases seen while at Johns Hopkins Hospital, Baltimore, during the winter 1924-5, and on a survey of the American literature undertaken because of the interest aroused by their study. Two of the cases are recorded in detail. Both were hospital patients in the public wards, and both from walks of life which in Britain would ensure their admission into the ordinary wards. It seems necessary to add this point, since it might be

¹ Received June 25, 1925.

suggested that the known differences in the type of patient admitted to public wards in America might account for the absence of cases in similar circumstances in Britain.

Records of Cases.

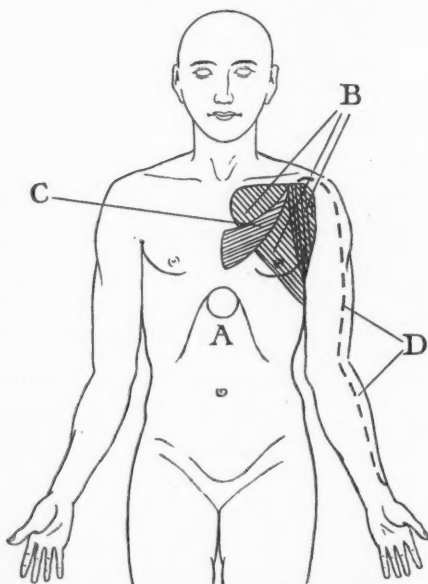
Case I. G. H., an unmarried woman, 58 years of age, was admitted to hospital on November 8, 1924, complaining of pain in the left breast and arm, shortness of breath, and fluttering of the heart. Her family history was negative, and she declared she had always been healthy. There was no history of rheumatic fever, chorea, or tonsillitis, and no definite story of any of the acute infectious diseases. At the age of 55 years (three years before admission) she began to notice that if she walked up a hill or hurried for a car she was seized with pain in her chest, radiating down both arms, particularly the left arm. The attacks of pain were associated with shortness of breath and an inability to speak clearly. She found that if she remained still when the pain appeared, relief occurred in three or four minutes. The pain in the chest was substernal and not epigastric. During the last two years these attacks had been more frequent and severe, and for the past seven months had been followed by deep muscle soreness so that pressure on, or movements of, the left arm and pectoral muscle caused discomfort. For one month prior to entry any emotional upset or trivial exertion would bring on the pain. There had never been any indication of cardiac failure.

One week before entry to hospital (twenty-three days before death) the patient was seized with a terrific attack of pain while at rest in bed. The pain was epigastric, radiated to the left arm, and was associated with severe dyspnoea amounting to orthopnoea. Soon after the onset she had two attacks of vomiting associated with eructations of gas. A physician who saw her about one hour after the attack began found her weak, cold, and almost pulseless. Morphine relieved the pain only temporarily and incompletely. The pain persisted with great intensity for at least forty-eight hours, then gradually disappeared. Restlessness, shortness of breath, and sleeplessness remained.

Upon entry into the hospital six days after the attack began she appeared worn and tired, and lay propped up in bed. Her face was pale, the extremities cold, and there was a dusky cyanosis of the nail-beds and lips. Her temperature was normal. The pulse was totally irregular, with occasional periods of bigeminal rhythm. There was oedema over the sacrum, abundant râles at the bases of the lungs, and the liver was enlarged and tender. The apex-beat was felt 11 cm. from mid-sternum; the heart's sounds were distant and feeble. No murmurs and no pericardial friction were heard. There was intense subcutaneous and deep muscular tenderness over the left side of the chest (see diagram on p. 46). Leucocyte count 10,200. Wassermann reaction negative. After admission the patient improved, but from time to time complained of dull aching in the left chest. Suddenly she began to have attacks of nocturnal mental confusion, and on November 28 (seventeen days after admission) she was again suddenly seized with pain, great dyspnoea, and tachycardia, and death occurred within twenty minutes, the symptoms and attitude suggesting a large pulmonary embolism. It had been noted on admission that her auricles were fibrillating, but the heart reverted to a normal rhythm later. The temperature was febrile on the third, fourth, and fifth days after admission, rising to 102° F. on the fourth day. Thereafter it varied between 99° and 100°, until shortly before death, when it rose for a short time to 102° F. The clinical diagnosis made was arteriosclerosis, occlusion of a large branch of the coronary artery, myocardial insufficiency, and terminal pulmonary embolism from mural thrombi in the right side of the heart.

Electro-cardiographic tracings were taken on November 10, 13, and 18. Two showed auricular fibrillation, and the third a normal rhythm. None of the peculiarities which have been noted in other cases of this kind were made out.

At necropsy the main pathological changes found were as follows: The heart was enlarged and dilated, weight 430 gm. The aorta was markedly atheromatous, the damage being far greatest in the descending arch and in the abdominal aorta, where large denuded areas lined with calcium salts were seen. The calcified patches continued into both iliac vessels. The ascending aorta and arch showed much less disease, but there was an area of calcification around the opening of the right coronary artery. The coronary arteries themselves both showed extensive sclerosis and calcification close to their origin, the lumen of the right coronary being almost occluded by thick calcareous plaques. A fine probe could be passed down this vessel for a distance of about 5 cm., where it met an



- A. Pain at commencement of acute attack.
- B. Tenderness in pectoralis region on admission to hospital.
- C. Late pain or soreness.
- D. Distribution of the anginal pain.

old organized and partly calcified thrombus. Below this blockage the wall of the vessel was practically free from sclerosis. A similar process was found in the descending branch of the left coronary artery (Pl. 11, Fig. 2), but here the thrombosis did not actually occlude the entire vessel. In the upper branch of the left coronary artery another organized thrombus was found, again not absolutely filling the lumen. The heart muscle was soft and flabby throughout; the left ventricle distended, and its walls thin (Pl. 10, Fig. 1). Near the apex of the left ventricle an aneurysmal dilatation of the ventricular wall was found. The endocardium in relation to this pouch was quite smooth, but in the actual apex of the ventricle one small grey friable thrombus was found. The right auricle contained an enormous thrombus completely distending the auricular appendix and part of the auricle as well. All the heart valves were healthy and smooth except for two small fatty patches on the aortic and mitral valves.

The lungs were greatly congested, and a large embolism was found to block completely the right pulmonary artery close to the hilum. This embolism was firm and of greyish-purple colour. The lymph glands at the roots of the lungs were found to be invaded by caseous tuberculosis, and there was also an area of active tuberculosis with much surrounding fibrosis in one lung.

The liver, which weighed 1,850 gm., proved normal on microscopic examination. The kidneys and renal vessels were free from disease. The spleen weighed 350 gm.

On further dissection of the heart the descending branch of the left coronary artery was largely filled with thrombus which was found histologically to be partly organized and partly unorganized. Early tunnelling had occurred in the organized zone (see Pl. 11, Fig. 2). In the wall of the left ventricle were multiple scattered areas of complete infarction, with necrosis of muscle cells, great surrounding vascularity and commencing fibrosis (Fig. 3). Cellular infiltration was abundant, but entirely of mononuclear type. Apart from the actual areas of infarction the remainder of the heart muscle appeared to be comparatively healthy and without any histological evidence of old-standing interstitial myocarditis.

Case II. A. L., a man aged 44, a laboratory attendant, gave a perfectly negative past history. He had never had rheumatic fever or syphilis, no attacks of pain in the chest or elsewhere, and no shortness of breath prior to the illness for which he was admitted. He was awakened suddenly at five one morning, early in February 1925, with intense pain in the epigastrium, which he thought was due to indigestion, and which was treated with sodium bicarbonate. Soon after taking the bicarbonate he vomited. The pain was described as very severe and seemed 'to grip his chest'. It radiated upwards to his clavicles, but did not extend to either arm. It was accompanied by considerable difficulty in breathing. He was first seen by a physician five hours after the onset of the attack. He was then extremely uncomfortable, pale, slightly cyanosed, and sweating. His temperature was 100.5° F.; pulse-rate 120, regular. The abdomen was board-like, and there was definite tenderness in the epigastrium. His leucocyte count was 12,040. Examination of the lungs revealed râles at both bases, especially the left, so that the question of early pneumonia at that base required careful consideration. The diagnosis appeared to lie between incipient basal pneumonia and perforated gastric ulcer. The physician who first saw the case discussed fully the possibility of coronary thrombosis, being himself very familiar with the clinical symptomatology of the condition from an experience of nine cases. Finally, however, this possibility was dismissed in favour of acute abdominal disease. The patient was, therefore, operated upon immediately, but on opening the abdomen nothing abnormal was found. After the operation the patient was extremely uncomfortable, complaining greatly of abdominal pain. Twenty-six hours after the onset of his pain a very definite *pericardial friction rub* was heard by several observers at the base of the heart. This persisted for eight hours, and then disappeared. His leucocyte count had gradually risen to 22,000, but dropped in three or four days to normal. He recovered well from the operation, but two weeks after the onset of his illness he was seized with another attack of intense precordial pain which did not last long and was controlled by morphine. His further progress was uneventful, at least until March 20, when the writer left Baltimore.

The Clinical Symptoms of Coronary Thrombosis.

The two patients whose clinical histories have been described illustrate most of the important symptoms, and also some of the difficulties and errors in diagnosis.

The clinical picture may now be analysed in greater detail, taking the history of these patients as a starting-point, and referring to some of the chief American articles on the subject, one of the best and clearest of which is that of Herrick (1912).

Previous History. There may be an antecedent history of angina pectoris (Case I), or the sudden coronary occlusion may be the first serious cardiac illness in a previously healthy person (Case II). In Wearn's series of nineteen patients in Boston, eight had already suffered from dyspnoea on exertion, six had had definite anginal attacks, while four had received no previous warning of cardiac trouble and came into hospital because of acute cardiac failure.

Onset. This is always abrupt—the patient may be well one minute and in agony the next. Wearn and other writers note that patients who have already suffered from anginal attacks know at once that they are faced with something quite unlike their previous experiences.

Pain. This is not a constant feature of sudden cardiac infarction, but occurs in by far the majority of cases. It is sudden, sharp, and knife-like in character, but differs from the pain of ordinary angina pectoris in its constancy and in its duration, if the patient survives the shock and does not die almost at once. It may remain for many hours, and even for several days, and here agrees closely with the description of 'status anginosus'. The distribution of the pain is irregular and peculiar, and this fact accounts for most of the errors of diagnosis in patients whose previous history is negative. The main localization may be exactly over the praecordium, or behind the sternum, or at the xiphisternum, or even in the epigastrium and right or left upper abdominal quadrants. When the pain is abdominal this and other symptoms mentioned below may strongly suggest perforated gastric or duodenal ulcer, cholelithiasis, or acute pancreatitis (cf. Case II). Two interesting papers in this connexion are those of Hardt, who describes a case closely simulating perforated gastric ulcer; and of Faulkner, Marble, and White, who discuss the differential diagnosis of coronary occlusion from cholelithiasis. Three cases are reported, in all of which gall-stones were suspected, but coronary obstruction was found in two of them where a fatal issue resulted.

The pain may remain local, or radiate in any direction; quite commonly it has the distribution to the arms observed in angina pectoris. Subcutaneous and muscle tenderness in the main areas of distribution of the pain may be extreme (cf. Case I). Such muscle tenderness and resulting spasm, if present in the upper abdomen, adds to the difficulties in differential diagnosis. A further character of the pain, noted almost universally in the literature, is the quite inadequate relief obtained by large or repeated injections of morphine.

Dyspnoea is invariable, but varies greatly in degree. Sometimes it is the only initial symptom, pain being absent. In such patients the attack of breathlessness is startling in its suddenness, and in the intensity of the choking sensation. The dyspnoea persists for many days, if the patient survives.

Colour of the face. This has been specially referred to by Libman and others,

and in the cases personally observed was certainly remarkable. Apart from the expression of anxiety or fear, the skin of the face has a peculiar earthy colour with a definite but light cyanosis, and is frequently covered with beads of perspiration. The facies is practically identical with that of acute shock, but differs in one important respect. It persists for long after the pain and distress have considerably ameliorated, a fact no doubt partly due to the acute cardiac failure which supervenes.

Vomiting is common, especially close to the commencement of the attack, and may lend false support to a wrong diagnosis of abdominal disease.

Cardiovascular symptoms and signs. These are naturally of critical importance in diagnosis. The general signs are those of rapid and acute cardiac failure, and when pain is absent, these may dominate the picture. The heart is generally found enlarged, and the cardiac sounds feeble and distant. Acute oedema of the bases of the lungs, acute enlargement of the liver, oedema of the feet or over the sacrum, and albuminuria develop with extraordinary speed. Two features require special mention. The acute pulmonary oedema, with abundant crackling râles at one or both bases, may strongly suggest an early pneumonic consolidation (cf. Case II). Libman has paid special attention to the acute hepatic enlargement, and states that thrombosis of the right coronary artery rather than the left may be suspected when the acute enlargement of the liver is very great.

Localized pericardial friction is an inconstant cardiovascular sign of very great significance, and almost diagnostic when found along with a suggestive history. Gorham (1920) has given an excellent account of the history and importance of this sign in a paper which includes a full and valuable bibliography, dating back to 1884. Only one British reference (Byrom Bramwell) is mentioned. Gorham himself reports six cases presenting the characteristic syndrome of coronary thrombosis, with necropsy records in three of them. In five of these patients a pericardial rub was detected clinically, developing within the first few days, generally of light intensity, transitory or recumbent, and localized to a small area. Gorham points out that this sign is very easily overlooked unless carefully and *repeatedly* sought for. In an unpublished case in private practice at Baltimore this sign was sought for by the physician with especial care. It appeared and disappeared within half an hour, and did not return.

In Wearn's nineteen cases this sign was only noted twice during life, but in the necropsy records of four other patients there was a fibrinous exudate and other signs of pericarditis, although no friction rub had been heard.

Longcope notes this sign as present in four out of twelve patients suffering from coronary occlusion.

Thayer, among a series of interesting personal observations on angina pectoris, describes four cases where the symptomatology strongly suggested sudden coronary obstruction. In one of these a soft friction murmur was audible over the præcordium on the fourth day.

Herrick also reports two patients in whom this sign was elicited.

Wearn states that pericarditis has been claimed by some to be present in all cases of cardiac infarction. Pathological examination of his cases showed, however, that many infarcts were deep within the myocardium, and no inflammation of the pericardium had resulted.

Thus this sign, although of the greatest importance when found, is not to be expected in all cases of coronary thrombosis.

Fever and polymorphonuclear leucocytosis. These two signs, which are invariably present, are chiefly important from their liability to lead the clinician astray, suggesting to him some acute inflammatory process in the lungs or abdomen. Fever may begin within twenty-four hours after the onset, but not earlier. The leucocytosis may be considerable, and surpass 20,000 (cf. Case II). The cause of the fever and leucocytosis is no doubt related to absorption from the dead and infarcted cardiac muscle.

Electro-cardiographic signs. Considerable attention has been paid to these by Herrick, Pardee, Robinson and Herrmann, Wearn, and others. It is evident that there is no special electro-cardiogram characteristic of coronary thrombosis, but many deviations from the normal may be found, and when grouped these may, with advancing experience, have some localizing significance and importance.

Course and Prognosis.

Sudden occlusion of main branches of the coronary arteries, whether from embolism or thrombosis, may have an immediate fatal result. This is particularly the case in embolism, which, however, is rare. Lamb describes one fatal case of complete embolism of the left coronary artery, and in his paper reviews the literature very fully.

Thrombosis, on the other hand, may have various end-results, which are divided by Herrick into four groups:

- (1) Cases of instantaneous death.
- (2) Cases of death within a few minutes or a few hours.
- (3) Cases of severity in which, however, death is delayed for hours, days, or months, or recovery occurs.
- (4) A group that may be assumed to exist with mild symptoms, not ordinarily recognized, and due to obstruction in the smallest branches of the arteries.

It is the third group which is of particular interest in this paper.

That recovery is possible for long periods from a serious cardiac infarction is shown by two cases in Thayer's series, and a number of others could also be referred to. Both of Thayer's patients almost certainly had coronary thrombosis. One, a labourer, survived at active work for three years. The other, a practising physician, lived and worked for thirteen years.

Ultimate death in these patients may be sudden, from return of symptoms of angina pectoris, or may be from gradual cardiac failure.

A fatal issue within a month or two after the initial attack may occur under

a variety of circumstances, but two complications depending on the cardiac infarction require special notice. Aneurysmal dilatation of the ventricular wall may end in actual cardiac rupture, but this is rare. More commonly, large thrombi may form, either on the site of the infarction, or in the auricles of the dilated and failing heart. In the first case personally observed, death occurred from a large pulmonary embolus, derived from the right auricle. Thayer, on the other hand, describes a remarkable case in which there were multiple emboli of kidneys, spinal cord, both iliacs, and one femoral artery, evidently from large mural thrombi on the infarcted wall of the left ventricle. This patient survived all these additional complications, and died suddenly eight years later.

It is evident from recent work that the course and prognosis of coronary thrombosis must to some extent vary with the previous state of the arteries themselves. Oberhelman and Le Count (1924) have shown that where coronary arteries are *gradually* narrowed by disease, a marked compensatory anastomosis between neighbouring branches may develop. Such an anastomosis must alter greatly the effects of thrombosis of the diseased branch.

Treatment.

Little need be said here about treatment, which follows the ordinary lines laid down by experience in angina pectoris.

A very clear account, in which full reference is made to the special problems of coronary thrombosis, is given in Thayer's recent paper.

Summary.

1. In sudden thrombosis of large branches of the coronary arteries there may occur, in patients who survive the immediate shock, a very remarkable clinical syndrome which deserves attention.

2. The main clinical features are as follows :

(a) Agonizing pain, of varying distribution, which lasts much longer than in the usual attack of angina pectoris.

(b) Dyspnoea, which may be extreme.

(c) A peculiar colour and appearance of the face.

(d) Immediate signs of acute cardiac failure—cardiac, pulmonary, hepatic, and renal.

(e) One sign which is inconstant, but almost pathognomonic in association with a suggestive history or group of symptoms, is a localized pericardial friction rub.

(f) Fever and polymorphonuclear leucocytosis.

(g) Various abnormalities in the electro-cardiogram.

3. Considerable difficulties in diagnosis may arise if the pain is localized to the upper abdomen, and an acute abdominal disease may be wrongly suspected.

4. The course and prognosis of this serious cardiac disease is very variable.

Many cases die at once or within a few weeks, but increasing experience in recognition of the condition has shown that some patients may survive in fair health for a number of years.

5. The recognition of the clinical syndrome should be fairly easy in patients who have previously suffered from cardiac complaints such as angina pectoris. The real difficulties in diagnosis arise when the coronary occlusion is the first evidence of cardiac disease in a previously healthy patient.

Thanks are due to Professor Warfield T. Longcope, Dr. C. S. Keefer, and many colleagues at Johns Hopkins Hospital, Baltimore, for making these observations possible during my stay there.

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DESCRIPTION OF PLATES.

PLATE 10, FIG. 1. Heart from Case I, showing the thinned-out infarcted area of the left ventricular wall, near the bases of the papillary muscles.

PLATE 11, FIG. 2. Incomplete section through the descending branch of the left coronary artery, showing organization and early tunnelling of the thrombus (Case I).

FIG. 3. Section of part of the infarcted wall of the left ventricle (Case I). Wide vascular spaces are seen in the midst of necrotic muscle, with well-marked early fibrosis around the margin.

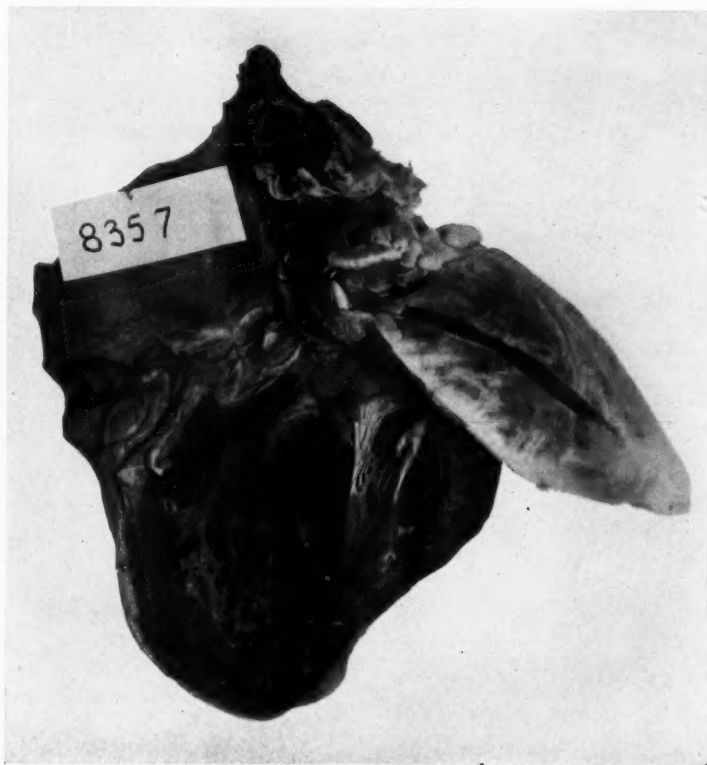


FIG. 1



FIG. 2

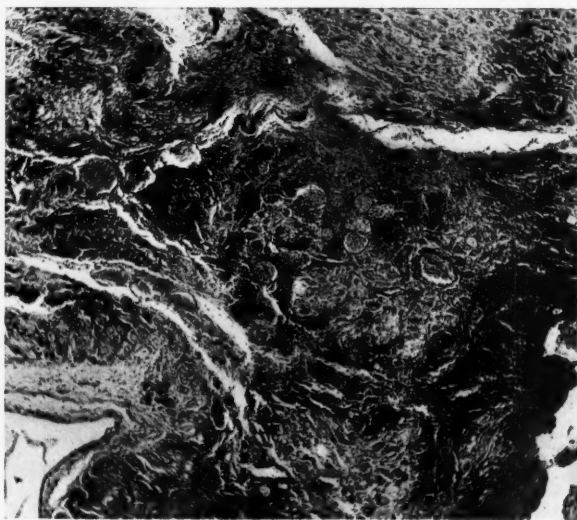


FIG. 3

THE EXCRETION OF CHLORIDES BY THE HEALTHY AND DISEASED KIDNEY¹

BY O. L. V. DE WESSELOW

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THE subject of the excretion of chlorides by the kidney in nephritis is still in such an unsettled condition that no apology is needed for a further examination of this aspect of renal function. The older belief that retention of chlorides in the body is entirely the result of renal inadequacy has lost ground, and with it the conviction that so-called renal dropsy is due primarily to a defect in the renal function. Some of the methods by which the excretion of chlorides by the kidney has been studied in the past are of doubtful validity, while others either involve an excessive amount of labour, or are exceedingly unpleasant from the point of view of the patient. A simpler method of examination is undoubtedly required, and it is with this object that the following study has been made.

The methods which have been employed in the study of chloride excretion by the kidney may be summarized under four heads:

- (a) Prolonged balance experiments (Widal and his associates).
- (b) Methods involving a comparison of the chloride content of the plasma or serum with the concentration of chloride in the urine, and the amount of chloride passed per unit of time (Ambard).
- (c) Methods aimed at eliciting a maximum concentration of chloride in the urine (Haldane, Adolph).
- (d) Combination of balance experiments with determinations of the chloride content of the serum (Veil).

Of these methods, the first is laborious and involves the administration of quantities of chloride in excess of the patient's excretory capacity, while it may give a false impression of renal inadequacy in conditions, such as lobar pneumonia or war-gas poisoning, in which chloride is abstracted from the blood and stored in the tissues.

The method of Ambard (1) permits of a rapid examination of the capacity of the kidney for chloride excretion, but is of doubtful value. The assumed identity of the so-called ureo-secretory constant for all substances excreted by the kidney may well be called in question in view of recent estimations of the

¹ Received June 6, 1925.

actual content of the blood in certain substances, such as ammonia, while the assumption of a low threshold for chlorides in interstitial nephritis is merely a restatement of the well-recognized fact that in this disease the chloride content of the blood varies inappreciably as compared with its urea content.

Attempts to elicit a 'maximum' concentration of chloride in the urine are not feasible in the sick patient, since large and nauseating doses of the salt are required, and in addition abstention from water is desirable. In view of the subsequent observations in this paper, some of the observed maxima under these conditions may, however, be detailed. Ambard has noted in man concentrations of 1 to 1.3 per cent. Cl, while Volhard (2) states that the healthy kidney's maximum concentration of chloride is approximately 1.1 per cent. Adolph (3) and Haldane (4) found maximal Cl concentrations of 0.295 to 0.308 M, and 0.29 to 0.33 M respectively. Bailey and Bremer (5) obtained concentrations of 1 per cent. NaCl in dogs, and Addis (6) in man concentrations varying from 0.82 to 1.35 per cent. Cl.

Addis does not believe that maximal concentrations in the sense of Ambard—'une concentration que l'on ne pourra faire dépasser à l'animal par aucun procédé, si artificiel soit-il'—have been obtained. He quotes experiments devised to elicit a maximum concentration of urea, in which the animal died from water deprivation at a time when the urea concentration in the urine was still rising. A further difficulty, though one of little importance in clinical work, is that 'maximal' concentrations of a substance can only be obtained when the concentration of other substances simultaneously excreted is kept at a low level. Thus Chaussin (7) has noted an interference between urea and chloride concentrations, and Haldane finds that the sum of the urinary concentrations of HCO_3 and Cl, when administered together, is equivalent to the maximum concentration of either—an observation which explains the retention of chlorides noted by Widal, Lemierre, and Weil (8) in bicarbonate oedema. It is probable, therefore, that true maximal concentrations have not been elicited, but for clinical purposes the study of 'submaximal' concentrations is of proved value. The general conclusion to be drawn is that in health the urinary Cl concentration may reach a figure of approximately 1 per cent., under conditions designed to stimulate the concentrating power of the kidney.

Lastly, attention may be called to the interesting work of Veil (9). The object of his researches being the study of the blood and tissue interchange—the intermediary chloride metabolism—little stress is laid on the nature of the renal response, nor do the results lend themselves to numerical expression. The importance of the interchange of salt and water between blood and tissues is stressed, and it is pointed out that the amount of these substances excreted by the kidney is ultimately dependent upon the NaCl plethora of the body and not upon the salt and water content of the blood. No direct relationship therefore exists between the NaCl content of the serum and the amount of the salt appearing in the urine.

The question of chloride excretion by the kidney has been intimately con-

nected with that of renal oedema since the work of Widal. To Widal, the oedema of the nephritic patient was the result of a primary chloride retention due to the renal defect, water retention being a secondary, but necessary, consequence if the chloride content of the body fluids was to be kept within a range compatible with life.

Certain difficulties are, however, met with if we accept this theory. Thus the chloride content of the plasma is by no means always at the high level that would be expected if inadequate renal elimination of chlorides was the primary factor. Secondly, the relationship between chloride and water retention is not always constant, and, in certain cases of interstitial nephritis quoted by Ambard, large gains or losses of chloride occurred without equivalent changes in the body-weight. Such discrepancies may be in part attributable to trifling variations in the chloride content of the large quantity of fluid present in the organism, but it would seem that they must in part be due to a 'dry' retention of salt.

Chloride depots which may be the site of such retention are known to be present in the body, the most important being the skin (10). If we admit that such 'dry' retention may occur, it follows that accumulation of chlorides in the body need not necessarily result in oedema.

Latterly, a tendency to attribute 'renal' dropsy to extra-renal causes has developed. According to Volhard and Fahr the early stage of oedema in nephrosis is accompanied by a concentration of the blood rather than a dilution. They suggest that the first step in the development of 'renal' dropsy is the passage of salt and water from the vascular system into the tissue spaces, owing to heightened capillary permeability. The apparent inability of the kidney to excrete water is the result of the diminished quantity of water present in the blood-stream, rather than of any renal defect. Nonnenbruch (11) also finds that in early glomerulo-nephritis the blood shows no dilution.

The factors governing the degree of hydration of the organism and the distribution of water between blood and tissue spaces remain obscure. It would appear that in the healthy individual an increase in the NaCl of the diet produces hydraemia and a definite gain in weight. After an initial lag, a balance is again struck between the ingestion and excretion of salt and water, though at a higher level of salt and water concentration in the blood and presumably in the body fluids. In glomerulo-nephritis a similar condition is present, though in an exaggerated form: the sodium chloride content of the blood may, according to Veil, reach a figure of 0.9 per cent., and extreme hydraemia is present. Any increase in the sodium chloride content of the blood is therefore, under these conditions, accompanied by an approximately equivalent increase in its water content, though in glomerulo-nephritis the amount of salt retained is out of proportion to the water retention, the chloride content of the plasma reaching a definitely abnormal level. Veil, however, finds that in interstitial nephritis, without oedema, the serum NaCl may rise after salt administration to a level as high as 1.0 per cent. without any corresponding dilution of the serum, an

observation which has been confirmed by Iversen (12). On the other hand, in certain conditions associated with excessive vomiting in which large quantities of chloride are being lost to the body, the loss of water may entirely fail to keep pace with the loss of salt, the plasma chloride falling to about half its normal level. The chloride concentration of the blood is therefore less constant than was at one time supposed, or, in other words, the water and chloride contents of the blood, and presumably of the body fluids, may vary independently of each other.

Another factor which influences the distribution of water in the body, and which has recently been the subject of considerable study, is the protein content of the plasma. As originally pointed out by Starling, the osmotic pressure of the plasma proteins, or rather their capacity for attracting water, is a by no means negligible factor in the secretion of lymph and excretion of water by the kidneys. Schade and Claussen (13) find that this 'onkotic pressure', as estimated by direct measurement, is lowered in renal oedema. In Eppinger's (14) opinion, the balance between blood and tissue fluids is upset by the passage of protein from plasma to tissue spaces—an albuminuria into the tissues—and oedema follows. According to Rusznyak (15) the relationship of the various plasma proteins is altered in oedema, a fact which had been previously noted by Epstein. The onkotic pressure of the plasma proteins is lowered by any increase in the proportion of total protein present as globulin or fibrinogen, the capacity for attracting water being less in the case of these two proteins than in that of albumin. Such an increase in the plasma fibrinogen is found in nephritis with oedema.

The relative importance of the roles played by sodium chloride and by the proteins in determining water distribution in the body is unsettled, but Loeb (16) in his excellent review of renal oedema concludes that the part played by the protein is altogether subordinate.

Experimental.

As a preliminary, a series of experiments was carried out on an apparently healthy individual, some of which are tabulated in Table I. The sodium and potassium chloride were taken in cachets, with the exception of the large doses (10 gm. and upwards), which were eaten with porridge. The experiments were in most cases begun two hours after breakfast, the composition of which, both fluid and solid, was in no way standardized, since the necessity of a preliminary period on a standard diet considerably limits the usefulness of such a test in clinical work. A few experiments were started three or four hours after the morning meal. The higher doses of potassium chloride were purposely limited to 10 gm., as compared with 17 gm. of sodium chloride, since it was considered that in the absence of adequate water for excretion, the potassium ion might in view of its known toxicity produce unpleasant symptoms. No such symptoms were, however, experienced with any of the doses taken. The plasma

TABLE I.

Dose.	Hour preceding Test.			1st Hr. of Test.			2nd Hr. of Test.			3rd Hr. of Test.			4th Hr. of Test.			Plasma Cl %.	Q ₁ .	Q ₂ .
	Cl %.	Amount in Grm.	Water in c.c.	Cl %.	Amount in Grm.	Water in c.c.	Cl %.	Amount in Grm.	Water in c.c.	Cl %.	Amount in Grm.	Water in c.c.	Cl %.	Amount in Grm.	Water in c.c.			
4 grm. NaCl (400 c.c. water)	0.46	0.74	173	0.28	0.72	258	0.75	0.72	97	0.84	0.53	64	—	—	—	—	—	—
4 grm. KCl (400 c.c. water)	0.55	0.72	131	0.18	1.10	613	0.56	1.41	252	0.78	0.90	116	—	—	—	—	—	—
"	0.85	0.63	74	0.38	1.15	303	0.38	1.42	375	0.79	1.04	132	—	—	—	0.366 1st hr. of test	44	16
(14 hrs. abstention from fluids)	0.75	0.29	39	0.70	0.37	53	0.81	1.02	126	0.96	0.70	73	0.97	0.21	22	0.369 2nd hr. of test	48	18
4 grm. NaCl (200 c.c. water)	0.75	0.45	60	0.72	0.47	66	0.87	0.50	58	0.91	0.59	65	—	—	—	0.372 2nd hr. of test	15	13
"	0.76	0.50	66	0.82	0.59	72	0.88	0.66	75	0.90	0.58	65	—	—	—	0.379 2nd hr. of test	16	14
4 grm. KCl (200 c.c. water)	0.82	0.58	71	0.68	1.13	167	0.78	1.11	142	0.84	0.69	83	0.88	0.51	58	0.373 2nd hr. of test	33	26
"	0.71	0.49	69	0.68	0.92	135	0.78	0.99	128	0.93	0.85	92	0.90	0.39	43	0.380 2nd hr. of test	24	19
"	0.84	0.50	60	0.64	0.80	126	0.85	1.08	127	0.94	0.67	71	—	—	—	0.373 2nd hr. of test	32	27
"	0.80	0.49	62	0.62	0.58	94	0.83	0.72	86	0.91	0.29	32	0.90	0.32	36	0.369 2nd hr. of test	24	20
10 grm. NaCl (200 c.c. water)	0.47	0.56	120	0.80	0.54	68	0.88	0.75	85	0.95	0.75	79	0.91	0.48	53	—	—	—
17 grm. NaCl (no fluid)	0.73	0.46	63	0.88	0.66	76	0.96	1.20	125	0.98	1.36	139	0.99	0.61	62	0.398 2nd hr. of test	20	19
(400 c.c. water per hr.)	0.71	0.27	38	0.92	0.54	59	0.94	0.86	92	0.90	1.26	140	0.94	1.17	346	0.389 2nd hr. of test	17	16
10 grm. KCl (no fluid)	0.69	0.31	46	0.66	0.71	108	0.67	1.33	199	0.79	1.33	169	0.96	1.03	108	0.375 2nd hr. of test	38	25
"	0.63	0.52	83	0.52	1.06	205	0.25	1.31	524	0.20	1.26	633	0.25	1.08	435	0.375 3rd hr. of test	36	7

$$Q_1 = \frac{\text{Cl passed per hour}}{\text{Plasma Cl } \% - 0.340}$$

$$Q_2 = Q_1 \times \text{concentration of Cl in urine.}$$

chlorides were estimated by the method of Austin and Van Slyke, the chlorides of non-albuminous urines by that of Van Slyke and Donleavy. The solutions employed were frequently checked against sodium chloride solutions of known strength. The blood was drawn direct into a centrifuge tube containing a little potassium oxalate, and the plasma immediately spun off in a centrifuge.

A consideration of the table leads to the following conclusions:

Administration of KCl leads to a more active diuresis and the appearance of larger quantities of chlorides in the urine than does that of NaCl, though the actual quantity of chloride given in the form of its potassium salt was less than that given as NaCl. This diuretic action of potassium has already been noted by Adolph and others.

There is a strong inherent probability that the chloride in the case of both KCl and NaCl ingestion would be excreted by the same mechanism, and this is borne out by the figures given. Thus the maximum amount of chloride passed in any one hour is for KCl 1.42 gm., for NaCl 1.36 gm.: the maximum concentrations attained in the urine for KCl 1.03 per cent., for NaCl 0.99 per cent.

The concentration of chloride attained in the urine shows, under certain limiting conditions, a very considerable constancy. Thus on the seven occasions on which 4 gm. of NaCl or KCl were ingested with a limited amount of fluid (200 c.c.) or after previous abstention from fluids, the following concentrations were obtained during the third hour: 0.84, 0.90, 0.91, 0.91, 0.93, 0.94, 0.96. With ingestion of much larger amounts of the salts these concentrations were not very appreciably exceeded. The maximum concentration noted for this kidney with the larger doses was 1.03 per cent.—a figure which agrees well with the maxima obtained by other workers. The average concentration to 4 gm. was as high as 0.91, and in one instance rose to 0.96. A relatively small dose of salt sufficed, therefore, to elicit a concentration within about 10 per cent. of the 'maximum', with a fair degree of constancy, provided that the fluid intake was not excessive.

The concentration of chloride in the urine after KCl ingestion is dependent upon the amount of water available for excretion, rather than upon the chloride content of the plasma in excess of the threshold value (0.340 per cent). Thus with plasma chlorides of 0.373–0.375 the urinary chloride concentrations vary from 0.25 to 0.85, with 524 and 127 c.c. of water passed during the hour.

Similarly the amount of chloride passed per hour after KCl administration shows no direct relationship to the plasma chloride concentration in excess of the threshold (Q_1), but appears to be largely determined by the amount of water available for excretion. With extreme grades of diuresis, the fall in the urinary chloride concentration is, however, out of proportion to the increased amount of water passed, with the result that the total chloride passed per hour shows a diminution.

An attempt to establish a constant (Q_2) by combining the factors—excess of chloride over threshold value in the plasma, amount of chloride passed per hour, and concentration of chloride in the urine—can hardly be regarded as successful.

In the Ambard ratio, the square roots of the two latter factors are utilized, but the evidence would seem to show that in the case of urea, at all events, the relationship in the blood and urine is more probably direct. By employing the square roots existing differences are minimized, and a false constancy is thus obtained. In addition, it may be pointed out that the unavoidable error of the chloride estimation, though small in comparison with the total quantity of plasma chloride, is very appreciable in ratios of this type, since it perforce falls upon the small amount of chloride by which the total chloride of the plasma exceeds the threshold.

The figures obtained show a greater constancy with sodium than with potassium chloride administration, but this is apparently merely the result of the comparatively poor response to the former salt. The body is indifferent to sodium chloride—a normal constituent of its fluids—while with potassium the excretory mechanism is called upon for a maximum effort. It results that, with potassium chloride administration, the rate of excretion is higher, even though the plasma chloride content may be lower than after sodium chloride dosage, the rise in excretion being effected by a mobilization of the body water, the incalculable factor for which it is impossible to allow in ratios of this type. Though a truer picture of the actual capacity of the kidney for chloride excretion may thus be obtained by the use of the potassium salt, no constant relationship could be established between the plasma chloride content and the urinary chloride. The optimal conditions for excretion are rarely hit off, since with too great or too small a diuresis the quantity of chloride passed falls away.

Taken as a whole the most constant factor in this series of experiments would appear to be the urinary chloride concentration after the diuresis has terminated. A figure approximating to the maximum is readily elicited by comparatively small and easily tolerated doses of chloride. The level of chloride concentration attained is for all practical purposes the same, whether the potassium or sodium salt is used, provided that the water intake is limited. As the highest concentration seen followed ingestion of the potassium salt, it was determined to investigate the effects of a dose of 4 gm. KCl in 200 c.c. of water on a series of normals. The potassium salt has the added advantage of eliciting a diuresis which it was hoped might shed light on the capacity of the kidney for excreting water. With a moderate intake of water, the third-hour concentration is not apparently diminished by the initial diuretic action of the potassium ion.

The series of normals examined (Table II) comprised eighteen healthy men and two women. In all cases the test was started between 10 a.m. and 11 a.m., no restrictions being imposed on the food or drink taken at breakfast.

Taking, in the first place, the question of the chloride concentration, it will be seen that in eighteen of the twenty individuals, or, with the previously studied case, in nineteen out of twenty-one, the highest concentration attained during the test exceeded 0.80 per cent. The maximum concentration of the series was

TABLE II.

No.	Dose.	Cl % before Test.	1st Hour.			2nd Hour.			3rd Hour.			Plasma, 2nd Hr. Cl %.
			Cl %.	Amount in Grm.	Water c.c.	Cl %.	Amount in Grm.	Water c.c.	Cl %.	Amount in Grm.	Water c.c.	
1	4 grm. KCl (200 c.c. water)	0.57	0.17	0.30	181	0.72	0.62	87	0.88	0.44	50	0.369
	"	0.18	0.23	0.71	308	0.78	0.66	85	0.84	0.44	52	—
	4 grm. NaCl (200 c.c. water)	0.72	0.83	0.66	82	0.89	0.59	66	0.88	0.28	32	0.373
	"	0.10	0.17	0.42	247	0.75	0.46	62	0.87	0.48	55	0.380
	12 grm. NaCl (no water)	0.60	0.78	0.23	30	0.95	0.56	59	0.96	0.69	72	0.380
2	4 grm. KCl (200 c.c. water)	0.75	0.87	0.76	87	0.89	1.43	161	1.03	0.96	93	0.372
3	"	0.89	1.01	0.82	81	1.03	1.57	153	1.07	0.95	89	0.375
4	"	0.33	0.63	0.17	28	0.90	0.67	75	0.98	0.50	51	0.377
	"	0.29	0.30	0.81	271	0.57	1.47	258	0.63	0.75	119	0.375
5	"	0.34	0.51	0.47	93	0.68	1.05	155	0.72	0.52	73	0.378
6	"	0.31	0.59	0.67	114	0.78	1.21	156	0.91	0.73	81	0.377
7	"	0.37	0.55	0.93	169	0.74	1.33	180	0.90	0.71	79	0.372
8	"	0.58	0.63	0.19	31	0.90	0.37	42	1.02	0.66	65	0.379
9	"	0.86	0.97	1.05	109	0.98	1.13	116	1.02	0.99	97	0.383
10	"	0.24	0.30	0.57	192	0.69	0.88	128	0.87	0.73	84	0.377
11	"	0.58	0.50	0.23	47	0.81	0.87	108	0.81	1.07	132	0.382
12	"	0.78	0.85	0.50	59	0.98	1.14	116	0.99	0.77	78	0.380
13	"	0.69	0.57	0.62	110	0.82	0.73	89	0.94	0.67	72	0.374
14	"	0.76	0.83	0.38	46	0.90	0.66	74	0.98	0.75	77	0.373
15	"	0.63	0.54	0.37	68	0.71	0.62	88	0.89	0.81	91	0.369
16	"	0.38	0.57	0.51	89	0.78	0.70	90	0.84	0.69	83	0.383
17	"	0.63	0.63	0.82	131	0.77	1.07	139	0.88	0.64	73	0.376
18	"	0.52	0.56	0.96	172	0.68	1.20	177	0.79	0.99	125	0.376
19	"	0.52	0.24	0.84	352	0.51	0.91	180	0.97	0.56	58	0.370
20	"	0.69	0.35	1.56	456	0.86	0.71	83	0.97	0.71	73	0.381
	"	0.29	0.19	0.76	401	0.75	0.96	128	0.86	0.62	72	0.379
21	"	0.55	0.51	1.22	241	0.68	1.62	239	0.84	0.79	94	0.363
22	"	0.55	0.54	1.79	332	0.80	1.54	193	0.85	1.01	119	0.363
23	"	0.31	0.35	0.55	157	0.53	0.73	139	0.58	0.57	98	0.361
24	"	0.17	0.10	0.31	316	0.75	0.59	79	0.85	0.74	87	0.375

Diabetic. Insulin.
Sugar free. U.C.T. 2.7
Diabetic. Insulin.
Sugar free. U.C.T. 2.9
Diabetic. 2 % sugar
during test. U.C.T.
3.6
Arteriosclerosis B.P.
205/125. U.C.T. 3.3

1-07. The initial concentrations before the chloride was administered varied from 0.10 to 0.89 per cent., and did not appear to exercise any very appreciable influence on the maximal concentration reached. In all, a concentration of 0.80 or over was reached in twenty-five out of twenty-eight examinations with the selected dose of chloride and water.

Further, in the few individuals examined on more than one occasion there would appear to be some indication of constancy in the response. Thus the two highest concentrations of the series were obtained in the same individual (Case 2), while the two lowest occurred in Case 4. No reason can be given for the low concentrations found in two individuals: in two of the three low results a diuresis was present during the third hour, but that such diuresis is not incompatible with the attainment of a concentration above the specified minimum is shown by Cases 10 and 22.

No relationship is to be found between the chloride concentration of the plasma in the second hour and the urinary chloride concentration of the second and third hours, nor between the plasma chloride and the amount of chloride excreted by the kidneys during the second hour of the test.

Of the three diabetics examined, two gave a normal response in spite of the low level of plasma chloride, which is characteristic of the disease and which is not improbably the result of excessive diuresis. The very large quantities of chloride passed by these two individuals during the course of the test is of interest, and is possibly significant of a hypertrophied condition of the kidney. In the third diabetic a low concentration was obtained, but 2 per cent. of sugar was present in the urine during the test.

It would seem then that a sufficiently constant concentration of urinary chloride can be attained by a test of this kind to serve as a basis for the examination of chloride excretion by the kidney in the clinic.

The variations met with in the group are such as are to be expected in any biological work. In the Addis ratio, for instance, in which, under very favourable conditions for urea excretion, the amount of urea excreted per hour divided by the urea content of the blood is used as an index of the quantity of functioning renal tissue, the variability would seem to be greater. The ratios in a group of healthy young adults varied from 36 to 64, and in the individual may range from 49 to 61. The variations in the group are no doubt in part attributable to the known variations in kidney weight in adults, but in the individual they can only be explained by temporary variations in the efficiency of the functioning tissue, and by the impossibility of exactly reproducing the stimulus to which the kidney is subjected. In a test of the concentration type the quantity of renal tissue does not come into question, but only the quality. No information is obtained as to the amount of active tissue, and such tests therefore find their most useful application in diffuse lesions such as are met with in nephritis, in which the entire renal tissue is more or less involved. The variations met with in the response are probably in part the expression of true differences of functional efficiency in apparently normal individuals. Such differences may be

partly inherent, but it is not unlikely that they are to some extent the result of purely temporary causes, such as the minor infections.

It remains to examine the response elicited by this method of examination in individuals suffering from various renal lesions.

Azotaemic Nephritis without Oedema.

The chief characteristic of this type of nephritis being an inability to pass a concentrated urine, the concentration of urinary chlorides during the third hour of the test might be expected to be low. Figures obtained from some of the cases suffering from this type of renal disease who have been examined are given in Table III, and it is at once obvious that a poor concentration is the rule. Impairment of the capacity for chloride and for urea excretion, as judged by the maximum figure obtained in the course of a urea concentration test, runs closely parallel. The fixity of chloride concentration throughout the test is very striking in the more severe cases.

The total quantities of chloride passed per hour under the stimulus are so small in some of these patients that it is difficult to see how a chloride balance can be maintained, unless the chloride content of the diet is very restricted. None of these patients, however, showed any oedema at the time of testing, so that if any gross retention of salt had occurred it had not been accompanied by water retention. Retention of water may apparently occur, since Ambard states that he has twice provoked acute pulmonary oedema in cases of interstitial nephritis by the administration of 15 grm. of NaCl.

In only two cases did the blood plasma show any appreciable variation from the normal. In the first of these the high figure of 0.404 was found in the second hour after 4 grm. of KCl had been given. According to Veil such hyperchloraemia is frequently met with in interstitial nephritis after salt administration, and no dilution of the blood occurs. With the heavy doses of sodium chloride which he employs, a prolonged and excessive rise of the plasma chloride was seen, but the protein concentration of the plasma remained constant: in the normal individual the rise in the plasma chloride that follows chloride ingestion is accompanied by abstraction of water from the tissues and hydraemic plethora. He apparently regards this abnormal response of the interstitial nephritic as the result of a defective interchange of chloride and water between the blood and tissues, rather than as the consequence of the renal defect. An actual examination of the chloride and water content of the tissue fluids is not of course practicable in these non-oedematous cases, but it would seem that the persistent hyperchloraemia may be regarded as the equivalent of the azotaemia and may fairly be attributed to the failure of kidney function. In interstitial nephritis the excretion of water remains good or even excessive, while the power of concentrating solids is greatly impaired: under such conditions the body fluids and blood will naturally become poorer in water and richer in dissolved substances, including sodium chloride. The real difficulty

TABLE III.

	Cl % before Test.	1st Hour.			2nd Hour.			3rd Hour.			Plasma, 2nd Hr. Cl %.	Blood Urea %.	Urea Con- centration Test. Maximum.	B. P.
		Cl %	Cl Amount in Grm.	Water c.c.	Cl %	Cl Amount in Grm.	Water c.c.	Cl %	Cl Amount in Grm.	Water c.c.				
1	0.21 0.20	0.23 0.20	0.28 0.27	121 134	0.21 0.22	0.15 0.22	72 101	0.22 0.19	0.13 0.14	60 75	0.404 0.377	0.147 0.307	1.25 0.75	172 140
2	0.14	0.18	0.12	71	0.24	0.18	76	0.24	0.16	69	0.368	0.075	1.5	125
3	0.20 0.10	0.20 0.26	0.12 0.25	65 97	0.20 0.33	0.15 0.26	78 80	0.25 0.33	0.55 0.71	220 218	0.352 0.368	0.032 0.073	1.0 1.4	226 185
4	0.22	0.25	0.25	100	0.30	0.35	116	0.33	0.34	105	0.375	0.051	1.35	115
5	0.34	0.33	0.21	66	0.47	0.44	93	0.53	0.41	77	0.372	0.047	1.75	117
6	0.47 0.12	0.15 0.23	0.35 0.65	232 286	0.51 0.70	0.58 0.80	114 114	0.70 0.76	0.43 0.79	62 104	0.379 0.383	0.029 0.025	2.0 2.1	170 172

lies in explaining how the chloride content of the blood usually remains at an approximately normal figure in these patients. Water excretion is frequently excessive, possibly owing to the diuretic action of the increased blood urea, and with inadequate power of salt concentration a general desiccation of the body with an excess of salt in the blood and tissues is to be expected, unless the salt intake is kept at a low level. The only patient in this series showing a hyperchloraemia suffered from excessive thirst.

In one case a diminished concentration of chloride was noted in the blood, but even in this case the diminution was slight. According to Veil the hypochloraemia of interstitial nephritis is significant of a pre-mortal break-down of the blood and tissue fluid interchange. He regards it as a possible basic factor in the production of the uraemic symptoms and as indicating a very grave prognosis. This view of the causation of uraemic hypochloraemia would seem to be quite untenable. Extreme hypochloraemia is frequently met with in severe cases of uraemia, but is, in my own experience, invariably associated with vomiting. Case 2, in the present series, had indeed suffered from severe vomiting up to two days before testing. The blood findings in these hypochloraemic patients are exactly those met with in high obstruction of the intestinal tract, and are most reasonably explained on the assumption of loss of hydrochloric acid in the vomit. As is well known, in high intestinal obstruction the plasma chlorides show a marked depletion, while the plasma bicarbonate is considerably above the normal figure. The usual explanation of this change is that Cl is abstracted from NaCl to form the HCl of the gastric secretion, sodium at the same time combining with carbonic acid to form bicarbonate which is returned to the blood. In azotaemic nephritis the position is complicated by retention of phosphoric acid in the blood, which of itself tends to deplete the bicarbonate of the plasma. The contrast between the chemical composition of the blood in two cases of interstitial nephritis taken shortly before death in uraemia will make it plain that a change of the same nature as in obstructive vomiting is present in these cases.

Plasma Cl %.	Plasma Inorganic P %.	Plasma CO ₂ Vols. per 100 c.c.
0.389	0.012	16
0.279	0.013	47

In the first case vomiting was absent, while in the second very severe uraemic vomiting had been a feature of the disease. With the similar grade of phosphate retention in both cases, the plasma bicarbonate should be equally reduced: actually it varies inversely as the chloride content of the plasma. The hypochloraemia is therefore of the same nature as that met with in obstructive vomiting; it is not an invariable concomitant of the terminal stages of uraemia, but is only seen in those cases in which vomiting is severe. Presumably, it is attributable to loss of hydrochloric acid in the vomit, rather than to any pre-mortal disturbance of the blood and tissue chloride interchange. Its prognostic significance is that of severe uraemic vomiting, and it is undoubtedly, as claimed by Veil, a very ominous sign, though occasional

temporary improvement in the patient's condition may occur. A close connexion between uraemic vomiting and hypochloraemia appears indeed to have been present in the patients examined by Veil, though, in default of any knowledge of the hypochloraemia of obstructive vomiting at that date, the connexion was not recognized.

To sum up, the kidney in interstitial nephritis shows, when examined by a chloride concentration test, an inability to concentrate chlorides running parallel with the failure of capacity to concentrate urea. In severe cases the concentration of chlorides in the urine after chloride ingestion is characteristically fixed—isosthenuria is present. The condition is of course equally well brought out by the older method of examination of the changes in the specific gravity of the urine which follow deprivation of fluid. The plasma chloride in interstitial nephritis appears to be inconstant: in some cases an excess of chlorides is present, in others marked hypochloraemia may be produced by vomiting.

Nephritis with Oedema.

The number of cases available for study was, unfortunately, small—thirteen in all. The results obtained are set out in Table IV, in which, for reasons to be discussed later, the patients are divided into two groups.

Group A.—The first group comprises three cases of typical parenchymatous nephritis. In Cases 1 and 3 the nephritis was apparently primary; in Case 2 a tuberculous lesion of the lungs had preceded its onset. In all three patients the onset had been characterized by rapid development of oedema and by early appearance of ascites. The duration of the dropsy had varied from three to five months when they first came under observation. The first patient's oedema disappeared during his stay in hospital; the second patient, who showed a marked defect of nitrogenous excretion, died in true uraemia, and *post mortem* showed very typical large white kidneys; the third remains oedematous and *in statu quo* at the time of writing.

Group B.—The second group comprises a great variety of conditions, but all the patients showed oedema of a greater or lesser degree associated with a renal lesion as evidenced by the presence of albuminuria and cylindruria.

Cases 1 and 6 gave a history of acute nephritis, followed by persistent oedema of the legs of twelve and nine months' duration respectively.

Cases 3, 4, and 7 were instances of pre-eclamptic toxæmia, and 10 was a true eclamptic examined twelve days after the cessation of convulsions.

Case 2 gave a history of oedema and albuminuria in four successive pregnancies, and for the three years following the last of these pregnancies had never been free from gross oedema of the legs. During a stay of eight weeks in hospital a loss of weight of 19 lb. occurred, but considerable oedema of the legs was still persistent on discharge.

In Case 5 a chronic nephritis was complicated by pregnancy; induced in the

TABLE IV.

A.		1st Hour.			2nd Hour.			3rd Hour.			Plasma. 2nd Hr.
		Cl % before Test.	Cl %.	Water c.c.	Cl %.	Amount in Grm.	Water c.c.	Cl %.	Amount in Grm.	Water c.c.	
1	9.12.24	0.021	0.015	10.5	0.027	0.0016	6.5	0.015	0.001	7	0.352
											Oedema fluid 0.391 % Cl. Ascitic fluid 0.407 %. Blood urea 0.062. U.C.T. 4.95
	22.12.24	0.046	0.052	26	0.091	0.022	24	0.090	0.013	15	
	8. 1.25	0.54	0.49	174	0.51	0.62	121	0.63	0.74	117	0.378
											Blood urea 0.018. Oedema subside- ing rapidly
	30. 1.25	0.14	0.19	29	0.42	0.25	59	0.54	0.20	38	0.373
											Blood urea 0.031. U.C.T. 3.75. No oedema present. Oedema re- curred 2 days later
2	3.12.24	0.015	0.019	39	0.018	0.007	40	0.023	0.008	38	—
											Ascitic fluid 0.412 % Cl. 30.11.24. 0.418 % 2.12.25. 0.413 % 3.12.25. 0.427 % 4.12.25
											Ascitic fluid urea 0.121 %. U.C.T. 1.25
3	20. 1.25	0.030	0.033	5	0.034	0.006	13	0.034	0.014	44	0.356
											U.C.T. 2.1. Gross oedema
	22. 1.25										0.340
											Ascitic fluid 0.385 % Cl. (Taken simultaneously, no previous KCl.)
											Gross oedema
											Ascitic fluid 0.055 % urea. Blood urea 0.052 %.
	31. 1.25										Ascitic fluid 0.391 % Cl. Gross oedema
	12. 2.25	0.032	0.049	41	0.039	0.008	21	0.060	0.028	48	0.348
											Blood urea 0.046. Oedema fluid (16.2.25) 0.390 % Cl. Gross oedema
	5. 3.25	0.045	0.042	49	0.052	0.097	38	0.054	0.022	41	0.355
											Blood urea 0.064. U.C.T. 2.2. Gross oedema
	3. 4.25	0.040	0.048	47	0.054	0.023	44	0.060	0.027	46	0.348
											Blood urea 0.074. Gross oedema

THE EXCRETION OF CHLORIDES

B.												Blood Urea.	U.C.T. %.	B.P.	Oedema.
1		0-59	0-56	0-09	16	0-65	0-67	104	0-87	0-43	50	0-389	0-022	3-4	180 + +
2	3. 9.24	0-38	0-16	0-42	264	0-51	0-57	112	0-64	0-47	74	0-388	0-034	2-2	185 + + + +
	30. 9.24	0-29	0-25	0-18	72	0-37	0-22	61	0-52	0-26	50	0-388	0-030	2-2	180 + + + +
3	27.10.24	0-42	0-23	0-31	135	0-44	0-50	115	0-56	0-38	69	—	—	—	+ + +
	24. 4.24	0-66	0-44	0-11	25	0-64	0-27	43	0-81	0-40.	50	0-397	0-016	2-4	180 + +
	14. 5.24	0-38	0-38	0-74	195	0-68	0-62	91	0-61	0-23	33	0-382	0-024	—	Before delivery
4		0-31	0-36	0-09	27	0-48	0-09	19	0-61	0-21	35	0-379	0-032	2-6	10 days after delivery 156 + +
5		0-16	0-23	0-09	38	0-33	0-18	57	0-32	0-14	45	0-389	0-079	1-4	236 +
6		0-21	0-12	0-32	265	0-26	0-20	78	0-30	0-31	103	0-404	0-046	1-5	105 +
7		0-19	0-15	0-08	54	0-28	0-10	37	0-41	0-15	38	0-381	0-039	2-5	160 + +
8		0-44	0-47	0-49	105	0-51	0-62	123	0-53	0-47	94	0-388	0-059	1-9	122 +
9		0-21	0-41	0-19	47	0-45	0-28	62	0-44	0-23	54	0-385	0-074	1-9	130 +
10		0-44	0-28	0-45	160	0-63	0-37	59	0-70	0-50	72	0-367	0-028	3-3	120 Tr.

third month, her condition three months after the abortion is so unsatisfactory that she has been unable to report for examination.

Case 9 was admitted for acute glomerulo-nephritis, and Case 8 for an exacerbation of chronic nephritis.

The second group is therefore composed of very heterogeneous material. In contra-distinction to Group A appreciable effusion into the serous cavities was absent in all cases.

Taking first the three patients included in Group A, it is obvious that the response to a dose of chloride during the stage of oedema is practically negligible. The concentration of chloride in the urine is inappreciable, and shows a well-marked fixity, while owing to the definite oliguria present the total quantity of chloride passed during the test can be expressed in milligrams. On the other hand, the ability to concentrate urea may be quite unimpaired, though so small a quantity of urine is passed that some accumulation of urea occurs in the blood. At first sight, therefore, a complete dissociation of the power of concentrating chloride from that of concentrating urea would seem to be present. Further consideration tends, however, to a modification of this view. It has been seen already that in the azotaemic form of nephritis a close parallelism exists between the impairment of the ability of the kidney to concentrate urea and to concentrate chloride, and an examination of the plasma chloride in two of these individuals suggests that this type of nephritis does not necessarily form an exception to the rule. In the third case no blood was obtainable owing to extreme oedema. In the two patients in whom the chloride content of the plasma was estimated during the stage of oedema, it was found to lie at the lower level of the normal range, even though a dose of chloride had been previously administered. In the one estimation (Case 3) in which no chloride had been ingested, the plasma chloride concentration approximated to the generally accepted 'threshold'. The chloride content of the ascitic and oedema fluids is, on the other hand, invariably high and may reach the extreme figure of 0.427 per cent. A marked disparity of chloride content in the plasma and tissue fluids is present, a disparity which does not extend to their urea contents. The absence of chloride from the urine may therefore be reasonably ascribed to the deficiency of chloride in the plasma.

It remains to ask ourselves, firstly, whether the chloride concentration in the plasma is actually below the level of the renal threshold, and, secondly, to what causes the impoverishment of the plasma in chloride is due.

A definite answer to the first of these questions can scarcely be given. Ambard, using his indirect, and probably fallacious, method of determining the threshold level for chlorides, found that even in normal individuals the threshold was constantly varying. Direct determinations of the threshold value can hardly be said to have been made, though there is a general agreement that in certain conditions, in which the blood is losing chlorides, such as lobar pneumonia or war-gas poisoning, chlorides practically disappear from the urine. The usually accepted level of plasma chloride at which this disappearance takes place is 0.340 per cent. On the other hand, there can be no doubt that appreciable

quantities of chloride may appear in the urine even when the plasma chloride has fallen to an exceedingly low figure. Veil has noted the presence of 0.07 per cent. Cl in the scanty urine of a patient suffering from sublimate nephrosis, in whom the plasma Cl had fallen to 0.217 per cent., and I have met with a case of interstitial nephritis in which, with reduction of the plasma to 0.256 per cent. by severe vomiting, 0.075 per cent. Cl was still present in the urine. In the light of such figures the existence of an absolute threshold, below which chlorides are not excreted at all, may well be doubted. The fact remains, however, that when the plasma chlorides have fallen to a certain level, chloride almost disappears from the urine, and it would appear probable that in these cases of parenchymatous nephritis the almost complete absence of chlorides from the urine may be accounted for in this manner.

Two possible explanations may be suggested for the diminished chloride content of the plasma in these patients. In the first case the fall in chloride concentration might be the result of defective excretion of water with resultant hydraemic plethora. The presence or absence of hydraemic plethora in such cases is by no means easy to determine, since the plasma solids may be considerably depleted by loss of protein in the urine, and since haemoglobin estimations spread over a prolonged period are an uncertain index to the blood-volume. It may be mentioned, however, that in certain anomalous cases of 'trench nephritis' with persistent oedema and marked ascites, but without the rise of blood-pressure characteristic of this disease and of acute glomerulo-nephritis, the haemoglobin findings were suggestive of a concentrated rather than of a dilute blood. Thus I have noted in one case a haemoglobin content as high as 108, and in another the haemoglobin fell from 108 to 94 per cent. during a period in which the patient lost 24 lb. of fluid. Both cases showed as reduced a urinary chloride concentration as those under discussion. It would seem then that in cases resembling closely those classed under Group A, the haemoglobin findings are suggestive of an oligæmia rather than of hydraemic plethora.

The only other probable cause of the diminution in the chloride content of the blood in these cases is an altered capillary permeability. In this connexion it is noticeable that an excess of chloride is present in the ascitic and oedema fluids as compared with the blood. In some instances the ascitic fluid chloride content may reach a very high level. The findings, therefore, suggest that a disturbance of chloride interchange is present, which leads to the banking up of chlorides in the tissue fluids. Even after chloride administration the plasma chloride concentration remains low; the vascular system is apparently unable to retain chloride. In agreement with the theory of undue capillary permeability, enormous quantities of fluid may be removed from these patients by continuous peritoneal drainage.

In Case 1 subsidence of the oedema was accompanied by a return of the plasma chloride to a normal figure, the urinary chloride concentration rising simultaneously to a satisfactory level. In spite of this apparently striking improvement in renal function, a high grade of albuminuria persisted, and

numerous tube casts were present in the urine: clinically, the condition of the urine showed little change.

It is suggested, then, that in this type of 'renal' dropsy extrarenal causes are actually at work: that the defect probably lies in an increased capillary permeability with resultant passage of water and salt into the tissue spaces and serous sacs; that the oliguria and extremely low concentration of chloride in the urine are the reflection of the poverty of the blood in water and chloride, and that it is doubtful whether dissociation of concentrating capacity for urea and chlorides is actually present.

The second group of oedematous nephritics presents a striking contrast to the first. In the majority of cases the chloride content of the plasma is higher than in the normal series, while the concentration of chlorides in the urine is in all cases fair, and in some attains an approximately normal figure. The presence of oedema cannot therefore be attributed to any defect in the power of chloride concentration. In interstitial nephritis lower chloride concentrations than these are met with in patients in whom no trace of dropsy is present.

On the other hand, the excretion of water, as far as it can be judged by the test employed, is poor. In six of these patients the water excretion during the three hours of the test averaged only 130 c.c., in three of the remaining four cases the oedema was subsiding at the time of the examination, and in the other patient (2) a period during which the oedema was stationary coincided with a poor water response. Coincidentally with the diminished water excretion, a smaller amount of chloride is passed during the test than in the normal, even in those patients in whom the chloride concentration is intact, while in those cases in which the concentrating power is impaired the amount of chloride passed during the three hours may be very low.

The cause of the relatively high plasma chloride concentration is obscure. Veil has noted that in war nephritis and in acute glomerulo-nephritis the plasma chloride may reach a very high figure. In one of his patients the extraordinary high level of 0.563 per cent. Cl was noted, while the oedema fluid obtained at the same time contained only 0.482 per cent. In my own cases no oedema fluid was available, but Veil's figures suggest that a reversal of the condition seen in the first group of nephritics may be present, and that the passage of chlorides from blood to tissues may be impaired.

In this second group the urinary urea and chloride concentrations run roughly parallel. Impairment of chloride concentration is associated with a low response to the urea concentration test. It may be concluded that both in interstitial nephritis and in various types of nephritis associated with oedema the evidence suggests that impairment of the ability of the kidney to concentrate urea is associated with defective chloride concentration, and that when one of these faculties is unaffected the other will be found to be intact. In the only group of cases in which dissociation of the two functions is apparently present, the failure to concentrate chlorides appears to be due to abstraction of chlorides from the blood, the movements of chloride in the body not being

determined solely by diffusion, as in the case of urea, but by processes which admit of dissimilar chloride concentrations in adjacent body fluids. It is of course recognized that neither in the case of chlorides nor of urea is concentration the sole factor to be considered in estimating renal function. Retention due to defective excretion inevitably results whenever water excretion falls below a certain minimum, determined by the amount of the substance produced or ingested, and by the capacity of the kidney to concentrate the substance in question. Urea retention may, for instance, be present in association with an excellent concentrating capacity in parenchymatous nephritis, or in cardiac disease, as the result of oliguria. In the functioning kidney there is always a tendency for the concentration of dissolved solids and the quantity of water passed to vary inversely, but there can be no doubt that with varying degrees of renal efficiency concentration is not entirely determined by the quantity of water passed. Though, by provoking diuresis, we can lower the concentration of any substance to an almost negligible figure, in diseased conditions, and according to most authorities even in health, there is an upper limit to the concentrations that can be reached. It is this upper limit that determines the amount of water which must be excreted if the waste products are to be eliminated. If it falls below a certain figure, even excessive diuresis, as in chronic interstitial nephritis, may fail to keep the waste products in the blood at a normal figure. It is for this reason that the study of concentration becomes such an important part of functional renal examinations, and from this aspect a kidney which is capable of concentrating a substance to the normal extent may be regarded as efficient, even though, owing to defective water elimination, retention of the substance in question may be present.

If speculation may be permitted, when the data are still inadequate, it may be suggested that the position in renal oedema is as follows:

In the first group of patients, clinically typical parenchymatous nephritics, in whom extreme oedema is associated with large effusions into the serous sacs, more especially the peritoneum, ingested water and chloride pass rapidly from the blood to the tissues owing to abnormal capillary permeability. The extent of this exudation may be judged by the enormous quantities of fluid which can be removed by peritoneal drainage. It is probable that the movement of fluid is to some extent conditioned by an abnormal distribution of chloride in the body, since the chloride content of the tissue and ascitic fluids is higher than that of the plasma. As a result of this movement the blood comes to be impoverished in chlorides and water. Such an association of oligæmia and hypochloraemia is now well recognized, being met with, among other conditions, in pneumonia, war-gas poisoning, and extensive superficial burns. The blood being deficient in water and chlorides, the kidney is afforded little opportunity of excreting these substances, and the urinary findings suggest a grossly deficient renal function in this respect. Actually, however, the oedema would appear to be of extra-renal origin, and, with return of chloride and water to the blood, excretion reaches an approximately normal figure.

In a second group, which includes acute nephritis, pre-eclampsia, and some cases of prolonged nephritic oedema without appreciable effusion into the serous sacs, a primary defect in water excretion is present with resultant reduction in the quantity of chloride passed even where the capacity for chloride concentration is not impaired. From the observations of Veil, and from personal experience in the acute glomerulo-nephritis met with in troops serving in France, it would appear that hydraemia is present in these patients. Water is presented to the kidney, but the response is poor. The oedema is of renal origin and is secondary to the failure of water excretion. Diminished power of concentrating chlorides in the urine is not the cause of the oedema, since the chloride concentration may lie within the normal limits, and since the very marked failure of concentration of chloride met with in interstitial nephritis is not necessarily accompanied by oedema. Larger quantities of chloride are passed by these patients in the course of the test than by interstitial nephritics who are quite free from oedema. For some unknown reason, the plasma chloride content in these patients is found to be at a somewhat high level after chloride dosage. No data are available as to the relative concentrations of chloride in plasma and tissue fluids, but an observation made by Veil suggests a relatively low content in the latter. If this proves to be the case, the distribution of water in the body may be determined in this group also by inequalities in chloride concentration, hyperchloraemia being accompanied by hydraemia. The absence of gross ascites may be stressed in this connexion.

On these somewhat speculative assumptions, chloride retention would cease to be the all-important factor in the production of oedema, but chloride distribution in the body would play a large part in determining the distribution of water between blood and tissue fluids.

Conclusions.

A method is described by which the capacity of the kidney for chloride concentration may be examined, and which appears to give sufficiently constant results in the normal to be of value in clinical work.

In interstitial, azotaemic nephritis the impairment of urea concentration and chloride concentration run parallel.

Nephritic patients showing oedema appear to fall into two groups. In one of these the plasma content in chloride is low, while the oedema fluid is rich in chlorides, and in these patients the oedema is apparently of extrarenal origin. In the other the chloride concentration is frequently good: it is suggested that in these patients defective water excretion is the underlying cause of the oedema.

It is doubtful whether true dissociation of the concentrating capacity of the kidney for urea and chloride occurs.

The causes of the variations met with in the percentage of chlorides present in the plasma of interstitial nephritics are discussed.

My thanks are due to the Medical Research Council, whose assistance has made this work possible, and to the Staff of St. Thomas's Hospital, who have allowed me access to the cases under their charge.

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SOME OBSERVATIONS ON THE ACTION OF BELLADONNA AND NEUTRAL FATS ON THE ACIDITY OF THE STOMACH CONTENTS¹

By W. MORRELL ROBERTS

(From the Manchester Royal Infirmary)

IN 1914 Boldyreff, by experiments on dogs, ascertained the occurrence of a phenomenon which he described as 'the automatic regulation of gastric acidity', whereby the acidity of the gastric contents is normally controlled by regurgitation of alkaline duodenal fluid, consisting of bile, pancreatic juice, and intestinal secretion, thus protecting the stomach against the full acidity of the gastric juice and maintaining an optimum reaction for gastric digestion. He demonstrated the presence of bile and of trypsin in the stomach contents.

Spencer Meyer, Rehfuess, and Hawk (1916) also identified these constituents in the stomach contents of man after the introduction of 0.5 per cent. hydrochloric acid into the empty organ.

Boldyreff's observations have been confirmed and extended in man by C. Bolton and Goodhart (1922) as a normal phenomenon, by the determination of the total and inorganic chlorides in addition to the acidity in the samples obtained in a series of fractional test-meals. They explain that the total chlorides represent the whole of the chlorine in the stomach contents from every source, whereas the inorganic chlorides originate mainly from hydrochloric acid of the gastric juice neutralized by the alkaline duodenal fluid. Duodenal regurgitation was found to occur at a definite period, but not always at the same time, during gastric digestion, this regurgitation depending upon relaxation of the pyloric sphincter, so that its presence or absence, as determined by the shape of the acidity and chloride curves, is a measure of the degree of tone or spasm of this sphincter, or of obstruction of the pyloric orifice.

This work has now been repeated and their results confirmed. The free and total acidity determinations on the test-meal samples were made by titration with decinormal caustic soda solution, using methyl orange and phenolphthalein respectively as indicators. The total and inorganic chlorides were estimated by Volhard's method. The results are expressed as the equivalent number of cubic centimetres of decinormal caustic soda solution, calculated on 100 c.c. of the samples.

¹ Received July 18, 1925.

Chart 1 is the type obtained in a normal case. There the acidity falls 42 points between $1\frac{1}{2}$ and $1\frac{3}{4}$ hours, the inorganic chlorides rising 41 points, the total chlorides showing no appreciable change, and bile appearing in the $1\frac{3}{4}$ hours sample. This indicates conclusively that alkaline duodenal contents have passed back into the stomach, thus neutralizing a portion of the hydrochloric acid, with the formation of an equivalent amount of inorganic chloride. The only change brought about in the concentration of the total chlorides is by dilution with the regurgitating fluid, which itself has a certain chloride concentration; hence only a slight fall in the total chlorides is apparent.

Chart 2 is from a case of complete pyloric obstruction where no regurgitation could occur. In this case the acidity and total chlorides rise steadily during the secretion of gastric juice, whereas the inorganic chlorides show very little increase.

In the light of these observations it seemed profitable to re-examine the action of belladonna and of neutral fats on gastric secretion, employing the same method of investigation. It has been believed that the fall in the acidity of the gastric contents after the administration of belladonna was due to a diminished secretion of gastric juice, but the fall may result, wholly or in part, from this reflux of duodenal contents into the stomach. Moreover, the practice of prescribing olive oil before meals in certain cases of reflex hyperacidity is based on the alleged reduction in gastric secretion said to occur after the ingestion of neutral fats.

Hydrogen-ion Concentration of the Gastric Contents.

Further, it appeared possible that information of greater value might be obtained by determining the hydrogen-ion concentrations of the test-meal samples instead of or along with their acidities by titration.

The determination of acidity by titration gives only an index of the capacity of a solution to neutralize alkalies; it gives no information concerning the concentration of free hydrogen ions, upon which its effective acidity at any given moment depends. The only method of expressing the acidity of the various samples satisfactorily must, therefore, be based on their hydrogen-ion concentrations.

For this purpose the method described by McClendon (1924) was tested over the required range by using fluids of known hydrogen-ion concentration obtained by mixing solutions of glycecoll and sodium chloride with decinormal hydrochloric acid, in varying proportions, according to Sørensen's table. The method itself depends on the determination of the percentage dissociation of quinaldine red, using a Kober's colorimeter.

The results show that the method is quite reliable for pH determination over this range, but it is very difficult to obtain consistent readings on the colorimeter at the lower limit of the scale when pH is less than 1.1.

The method was applied to several of the test-meals, including that shown

on Chart 1, and it was found that the hydrogen-ion concentration for the most part followed the acidity curves so closely that the method was not pursued further.

Readings on Colorimeter.	pH (corresponding to Average Colorimeter Reading).	pH (Sørensen).
2.8 2.7 2.5 2.8	2.7	1.14
5.1 4.9 5.0	5.0	1.42
8.0 8.0 8.0	8.0	1.64
13.9 13.6 13.7 13.9 13.9	13.8	1.89
26.5 26.4 26.5 26.5	26.5	2.26
		2.279

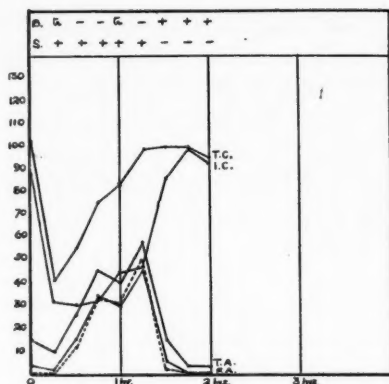
Belladonna and Atropine.

Conflicting results have been obtained by the various workers on this subject. Crohn (1918) was unable to produce any reduction in gastric acidity by means of atropine, and Bastedo (1920) found acidity lowered only in hypersecretion in the post-digestive period. On the other hand, Bergmann (1913), Mathieu (1914), Schmidt (1914), and Chiari (1915) all obtained positive results.

Craven Moore and Kilroe (1910), using the Ewald test breakfast, found that the administration of belladonna leads to a considerable reduction in gastric acidity, the greatest effect being produced in cases of hypersecretion, and concluded that this result was due to a diminished secretion. Since they found no appreciable variation in the volume of the gastric contents along with this diminution of secretion, they concluded further that the rate of emptying of the stomach was delayed. More recently, Bennett (1923) also found consistent diminution of gastric acidity with atropine administered orally. Bolton (1923) states that the action of atropine is to diminish gastric secretion more particularly in the fasting stomach, but that its beneficial effect during digestion is due to its relaxing action on the pylorus, thus facilitating duodenal regurgitation.

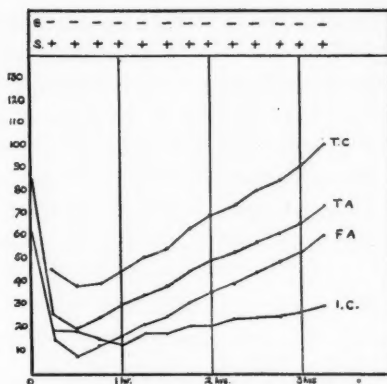
The present series of cases examined showed considerable differences in their reactions to these drugs, though the effect in each individual case remained constant. In more than half the cases the acidity was reduced; in one patient a rise in acidity resulted; in the remainder it was impossible to trace any effect, for the acidity was reduced in some samples but raised in others. The most marked effect was obtained in severe cases of reflex hyperacidity in duodenal ulcer and appendicular disease.

CHART 1.



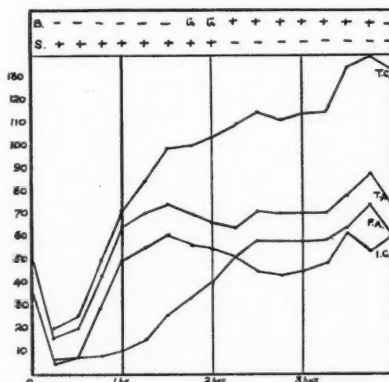
Patient A. Male. Aged 42. Diagnosis: Gastric ulcer. Dotted line represents hydrogen-ion concentration.

CHART 2.



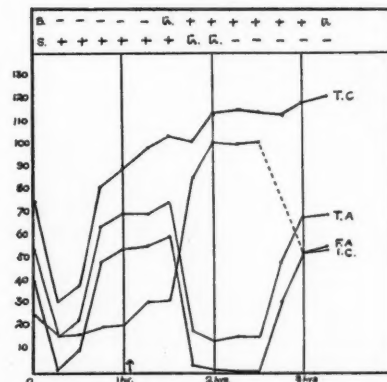
Patient B. Male. Aged 40. Diagnosis: Pyloric stenosis. The stomach was not empty after 3½ hours.

CHART 3.



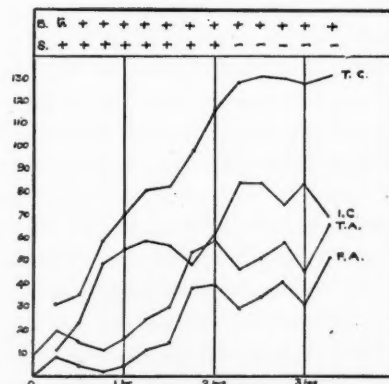
Patient C. Male. Aged 40. Diagnosis: Reflex dyspepsia (from appendix).

CHART 4.



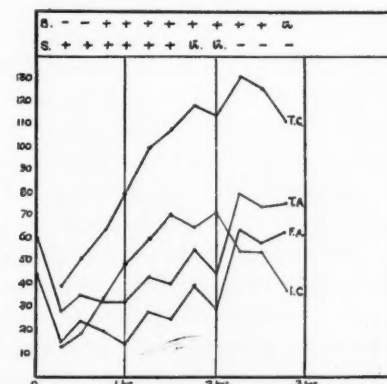
Patient C. Tinct. belladonnae (A) x given at point shown by arrow.

CHART 5.



Patient C. Atropine sulphate gr. $\frac{1}{160}$ given 10 minutes before meal.

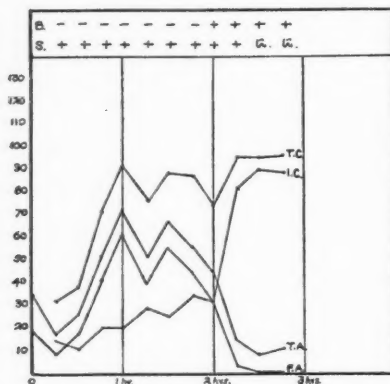
CHART 6.



Patient C. Tinct. belladonnae (A) xv given 10 minutes before meal.

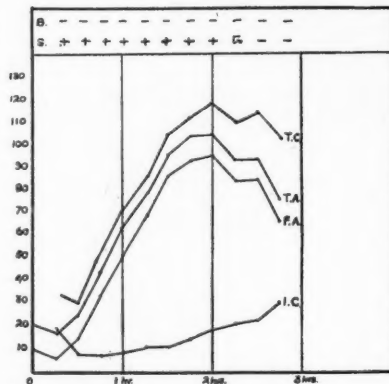
Charts 3-6 are from one such case of reflex appendicular dyspepsia. It will be observed that in Charts 3 and 4 the general course of the curves for the first $1\frac{1}{2}$ hours is very similar, but that the effect of the belladonna given at the end of an hour in the latter meal then becomes apparent, for a very definite duodenal regurgitation occurs and the acidity remains within normal limits for the next hour. In Charts 5 and 6, atropine and belladonna respectively were given ten minutes before the meals, and the curves show that an intermittent regurgitation from the duodenum occurred throughout.

CHART 7.



Patient D. Male. Aged 41. Diagnosis:
Gastric ulcer.

CHART 8.



Patient D. Almond oil $\frac{3}{4}$ (emulsified) given
half an hour before meal.

It appears from a consideration of these curves, which are typical of those obtained in cases of hypersecretion, that the action of belladonna and atropine in reducing acidity is by relaxing the pyloric sphincter, thus allowing neutralization to occur earlier or more frequently than in the ordinary course, this being indicated by the earlier appearance of bile in the samples and by the sudden or gradual rise of the inorganic chloride curve.

On the other hand, the total chloride curve appears to be almost unaffected. If this curve represent the gastric secretion it would seem to follow that there has been no inhibitory action in this direction. But it should be noted that the stomach tends to empty more rapidly after administration of atropine or belladonna, as is frequently shown by the disappearance of starch from the samples at an earlier stage in the meal, and by the greater difficulty which may be experienced in drawing off a full 10 c.c. sample every $\frac{1}{4}$ hour. In these circumstances, a smaller secretion of gastric juice will suffice to raise the total chloride figure to the same level, whilst the acidity is prevented by the duodenal regurgitation from rising proportionately. In the fractional test-meal method one is unable to estimate the volume of the stomach contents present at any moment, so that one cannot determine precisely the amount by which secretion is increased or diminished. It is thus possible that in some measure the effect

may be a diminution of gastric secretion. The duration of the action varies from one to four hours.

Atropine sulphate acts more effectively than an approximately equivalent quantity of tincture of belladonna.

The therapeutic indication following from these results is that belladonna or atropine may be recommended in cases of digestive discomfort where hyperacidity is a factor, and though some cases do not respond, those with high acidity of reflex origin are likely to be benefited.

In the table on p. 80 the total acidity and inorganic chloride figures are shown in detail for each meal from one hour to three hours inclusive. The figures in the control meals represent the average of two or more meals.

Some idea of the extent to which any change in the acidity is due to a variation in the degree of neutralization occurring may be obtained by a consideration of the inorganic chloride figures along with the corresponding total acidities, since the inorganic chlorides are themselves a measure of the neutralization.

Neutral Fats.

It appears to be universally agreed that the emptying of the stomach is retarded by the administration of fats. In addition, Ewald and Boaz (1886) found that the acidity of the stomach contents was diminished. Pavlov showed that the effect of fats in dogs was to produce a secretion small in quantity and weak in power. Boldyreff (1908), experimenting on dogs with gastric fistulae, found that fats cause regurgitation of bile and pancreatic juice into the stomach, but later (1914) describes this regurgitation as a normal phenomenon during the ordinary course of digestion.

In the present investigation, the usual procedure in the oil meals was to withdraw the fasting contents from the stomach and to give an ounce of olive oil or of sweet almond oil, followed by the gruel meal half an hour later. In some cases the oil was emulsified with tragacanth, the whole being made up to about three ounces with water, in order that it might be more palatable to the patients and that any effect might be intensified by thus greatly increasing the surface of the oil.

It should be observed, before considering the results obtained, that oil was present in almost every sample withdrawn during the meals, thus demonstrating that all the oil given had not passed into the duodenum in the half-hour elapsing between its administration and the taking of the gruel.

As was the case with belladonna and atropine, great variations were found in the degree of reaction of the different patients, though each individual usually gave similar results on repetition.

The constant reduction in acidity remarked by other workers was not substantiated. It must be remembered, however, that, as for example in the

work of Craven Moore and Ferguson (1909), the results were obtained by the Ewald test-meal, in which the whole of the stomach contents is withdrawn at the end of an hour. In the present series about 60 per cent. of the cases showed a fall after one hour, but in practically every case either the acidity after two hours was above that found at the corresponding time in the control test-meal, or where the control meal was finished in less than two hours without any abnormal acidity, hyperacidity developed after oil had been given and the meal lasted beyond two hours.

In several instances the composition of the samples towards the end of the oil meal suggested that the contents of the stomach consisted almost entirely of gastric juice, whereas this was not noticed in the control meals. This observation may be explained on the assumption that a reflex secretion of gastric juice occurs as a result of the action on the duodenal mucosa of the oil soaps formed after hydrolysis of the fat by the pancreatic juice. Babkin and Sawitsch (1908) found that such a secretion occurred in animals after the direct introduction of oil soap into the duodenum.

There was no evidence of any fat-splitting activity in the stomach itself, for the difference between free and total acidity showed no appreciable deviation from that obtained when no oil was given. If the oil were hydrolysed in the stomach, the free fatty acid should show in the total acidity, the free acidity (i. e. free hydrochloric acid) being unaffected.

Contrary, too, to the results of other investigators, there appeared to be less tendency for regurgitation from the duodenum to occur, since the inorganic chlorides were usually reduced in quantity, and bile did not appear until a later stage. The general course of the total chloride curve showed little modification after oil. Since one effect of oil is to retard emptying of the stomach, thereby increasing the volume of its contents as compared with the volume after the same interval of time in a meal without oil, a lower total chloride figure would result if the secretion remained the same. Hence there may be some increase in secretion in those cases where any fall occurring in total chlorides is less than proportionate to the increase in volume of the contents. Here the difficulty pointed out in discussing the action of belladonna occurs again; it is impossible accurately to gauge the increase or decrease in the amount of the secretion unless the volume of the gastric contents can be determined.

The results corroborate the previous observations of the retardation of the emptying of the stomach. Starch could often be detected at a later period in the meal, and the time during which samples could be obtained was prolonged.

Any difference that could be traced between the effect of almond oil and olive oil suggested that almond oil causes a greater initial fall in acidity and a subsequently greater rise. The same may be said on comparing oil given with the meal with oil given before the meal, for in the former case the initial acidities were lower and the later ones higher than in the latter. There was no constant relationship apparent between the actions of oil and of belladonna or atropine in the same patient.

9	Male. Aged 30. Appendicular dyspepsia	Control Emulsified olive oil	8	43	11	54	8	81	—	8	31	—	8	59	—	8	71	—	7	77	—	—	—	—	—
10	Male. Aged 17. Neurasthenia and recurrent appen- dicitis	Control Emulsified olive oil	16	84	46	64	29	78	45	37	21	64	40	77	—	48	24	—	56	28	—	—	—	—	—
11	Male. Aged 35. Intestinal stasis causing dyspepsia	Control Emulsified olive oil Emulsified olive oil (mixed with meal) Emulsified olive oil	50	58	56	57	57	56	—	—	—	—	—	—	—	78	43	—	14	100	—	12	100	13	80
12	Male. Aged 39. Appendicular dyspepsia	Control Emulsified al- mond oil	39	28	41	43	33	50	—	25	72	—	—	—	—	—	—	—	—	—	—	—	—	—	—
			32	36	55	43	55	46	25	25	72	—	12	85	—	—	—	—	—	—	—	—	—	—	—
			58	19	73	23	50	27	83	32	89	37	90	36	58	59	8	44	—	—	—	—	—	—	—

No single case showed every point mentioned, so that it is impossible to demonstrate the effects completely without unduly multiplying the number of charts, or constructing a composite chart from several cases. However, a comparison of Charts 7 and 8 will reveal the most striking feature, viz. the inhibition of duodenal regurgitation with the resulting increase of acidity.

Summary.

1. The observations of Bolton and Goodhart on the occurrence of duodenal regurgitation as a normal phenomenon in gastric digestion in man have been repeated and confirmed.

2. The hydrogen-ion concentrations of the samples obtained in the test-meals have been estimated and found to follow closely the acidities as determined by titration.

3. The effect on gastric acidity of administration of atropine and of belladonna has been re-examined and found to vary considerably in degree, being most marked in cases of hypersecretion. The acidity is lowered by increased regurgitation from the duodenum, consequent upon a relaxation of the pyloric sphincter, and probably to some extent by a diminution of gastric secretion. The stomach tends to empty more rapidly.

4. The effect of oil on gastric acidity also varies in intensity in different patients, but there is a tendency for the emptying of the stomach to be delayed and for duodenal regurgitation to be inhibited. As a result the acidity rises above the normal, though this may not manifest itself until digestion is well advanced. There is, in addition, some evidence suggestive of increased gastric secretion.

This work was carried out whilst I was acting as House Physician on Dr. Craven Moore's unit at the Manchester Royal Infirmary. For his suggestion that the investigation be undertaken and for his valuable guidance and criticism during its progress I offer him my sincere thanks.

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ON SULPHAEMOGLOBINAEMIA¹

By LAWRENCE P. GARROD

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SULPHAEMOGLOBINAEMIA is a disease which, owing to its rarity, has received little attention from investigators. Its scanty literature chiefly comprises records of single cases, and such observations as have been made lack the authority which is conferred by consistent findings in a series of patients. The well-ascertained facts as to the disease are briefly as follows: It occurs almost exclusively in females, usually in early adult life, and consists in attacks of cyanosis, varying in frequency and duration, and continuing at intervals for years. During intervals between attacks a slight cyanotic tinge may persist, or the patient's appearance may be normal. The 'cyanosis', when present, is of a peculiar leaden-blue colour, deepening in the mucous membranes almost to black at the height of an attack, and it is unassociated with dyspnoea, with any discoverable lesion of the heart or lungs, or with any notable alteration of the blood-count. Other symptoms usually present are weakness, constipation, and headache. It is known that the change in the blood (which is of a chocolate-brown colour when withdrawn during an attack) is due to the presence of sulphaemoglobin. This pigment is intracorpuseular, the colour of the serum being normal. The disease can only be diagnosed by spectroscopic examination of the blood, and it requires then to be distinguished carefully from methaemoglobinaemia, a disease the clinical features of which are very similar.

It is well established that methaemoglobinaemia is the consequence of habituation to drugs of the coal-tar group, but the causation of sulphaemoglobinaemia is unknown, unless the hypothesis put forward by Mackenzie Wallis in this Journal in 1913 be correct. The aim of the present paper is to record some observations which appear to confirm this hypothesis. Mackenzie Wallis's study of the disease, based on a series of five cases (the largest number hitherto accumulated by any single observer), yielded the following data.

It was found that a strong reducing substance was present in the urine, blood, and saliva of all the patients. It could be demonstrated in the blood by adding the serum to normal whole blood, in which the spectrum of reduced haemoglobin appeared within a short time. It had previously been shown by Wood Clarke and Hurtley that powerful reducing agents greatly accelerate the production of sulphaemoglobin from oxyhaemoglobin treated with minute traces of sulphuretted

¹ Received June 25, 1925.

hydrogen. In their own words—'This experiment suggests that possibly the etiology of the disease known as sulphaemoglobinaemia may lie rather in the presence in the blood of some hitherto unascertained reducing agent or of some known reducing agent in abnormal amount which allows a normal trace of sulphuretted hydrogen to act on the blood, than in the presence of an excess of this gas.' It is here assumed that a sufficient quantity of sulphuretted hydrogen is normally generated in the bowel to provide for this change should the intermediary substance, or reducing agent, be present in the circulation.

Exhaustive search was therefore made, with the assistance of Dr. Mervyn Gordon, for an infection by an organism capable of forming such a reducing substance, with the result that in the saliva of all these cases, to which attention was directed by the fact that it was found to contain nitrites in considerable amount, there was found an organism which was named the 'nitroso-bacillus'. This had characters so peculiar that it could hardly be confused with any other organism known to human pathology. It was a somewhat oval, non-motile Gram-negative bacillus of exceedingly slow growth, the optimum temperature for which was found to be 25°C. It grew in all ordinary nitrogenous media, but fermented no sugars; it slowly reduced neutral red, and liquefied gelatin; its colonies on solid media, which appeared about the fourth day, were small, round, and semi-translucent. By growing it in solutions containing 'necessary salts' and various nitrogenous compounds it was found that the organism disintegrates a number of complex amino-acids, with the formation of nitrites. This phenomenon is the clue to its identity; the formation of nitrites in fluid media, which invariably takes place, can readily be demonstrated by the addition of Ilosvay's reagent, which produces a bright crimson colour. This organism was found also to produce in fluid cultures a reducing substance having the same action on blood as the serum of the patients from which it was obtained. It was obtained from the saliva of all the five cases, sometimes in pure culture, and it was absent from numerous cultures from the saliva of normal individuals investigated as controls. It was not found in the stools. Other experiments by which the properties of this organism were determined will be found in the original paper.

It may be noted that Long and Spriggs have subsequently investigated a case of sulphaemoglobinaemia from this standpoint, and failed to discover the nitroso-bacillus in the saliva. The faeces were not examined for the organism.

Case Reports.

The writer has had the opportunity of investigating two cases of sulphaemoglobinaemia, and these are chiefly of interest in that the nitroso-bacillus was found in the faeces.

Case I. M. A. C., unmarried, aged 41, a secretary, was admitted to St. Bartholomew's Hospital under the care of Dr. Morley Fletcher on January 4, 1923. The history of her illness was that since 1906 she had suffered from

what were described as 'heart attacks'. The features of these attacks were a bluish-grey colour of the skin, increasing in intensity, headache, and abdominal pain. Vomiting sometimes occurred, and there was usually slight shortness of breath. She was always severely constipated. The attacks had increased in severity and frequency since 1921, when she was overworked.

Past history. Scarlet fever and measles; deafness since childhood. Found in 1913 to have a floating kidney. The catamenia had been irregular, with excessive loss and much pre-menstrual pain.

Condition on admission. A somewhat thin woman with a muddy complexion and mucous membranes of a bluish tinge. Eyes natural, but intolerant to light. Teeth healthy, but marked furring of the tongue and feto-oral. Heart and lungs natural. Nothing abnormal found in the abdomen except a freely movable right kidney. Limb reflexes natural. No clubbing of the fingers. Urine, sp. gr. 1025, acid; no albumin, sugar, bile, or indican.

On January 15 the cyanosis greatly increased, with headache, photophobia, and nausea. There was no dyspnoea. The attack lasted for twelve hours, and was apparently relieved by the continuous intranasal administration of oxygen. Further similar attacks occurred on the 19th and 25th. On the 23rd the blood was examined spectroscopically, and found to contain methaemoglobin. On the 31st a postal package addressed to the patient was found to contain 'Antikamnia' tablets. On being questioned, she admitted having taken these tablets for twenty years, chiefly for the relief of menstrual pain; she had not observed that her attacks of cyanosis bore any relation to taking this drug. She agreed, however, to forgo its use in future. No further severe attacks occurred, but the cyanosis persisted in varying degree, and on February 9 spectroscopic examination of the blood revealed the presence of sulphaemoglobin. This was also found on four subsequent occasions, the examinations being carried out by Dr. Mackenzie Wallis and Dr. Hurtle. Whereas on January 23 the band in the red disappeared on the addition of ammonia or ammonium sulphide, on February 9 and subsequently it was unaffected by this treatment; the passage of carbon monoxide shifted the band from 615-25 to 605-10. This patient's blood had therefore contained both methaemoglobin and sulphaemoglobin within a period of a few weeks, an association of conditions which has not hitherto been recorded.

Several blood-counts gave an average of:

Red blood cells	4,700,000 per c.mm.
Haemoglobin	66 per cent.
White blood cells	4,900 per c.mm.

The fragility of the red cells was normal.

On February 13 the faeces were examined. The specimen was liquid, of brownish-green colour, with an abnormally foul odour. Cultures by a method which is described later yielded a profuse growth of the nitroso-bacillus.

The saliva contained nitrites in small amount; plate cultures on legumen-agar incubated at 20° C. yielded no growth of the nitroso-bacillus; this examination was performed once only. Agglutination and complement-fixation tests with the patient's serum and an emulsion of the nitroso-bacillus as antigen were completely negative.

The patient was at first treated with aperients and Plombière's douches, with some degree of improvement. The administration of an autogenous vaccine of the nitroso-bacillus was begun on April 13, doses from 10 to 500 millions being given between then and May 10: the improvement continued, and at the end of this period the cyanosis had disappeared; the examination of the blood for sulphaemoglobin was also negative. The patient had gained 4 lb. in weight, and left the hospital apparently well.

In the following year she reported, in response to an inquiry, that the attacks

of cyanosis had recurred. Two further series of vaccine doses, from 100 to 20,000 millions each, were then given by Dr. H. V. Deakin, of Falmouth, the administration of twelve doses being extended over a period of several months. The attacks became less frequent, and finally ceased; the patient reported, in August 1925, that she had been in good health, and had had no cyanosis whatever since the previous year.

The most remarkable feature of this case is the apparent association of methaemoglobinaemia due to drug addiction with sulphaemoglobinaemia. From the data available it can only be concluded that one or more of the severe attacks of cyanosis observed in hospital were due to the former cause, and that after its removal she remained a case of sulphaemoglobinaemia pure and simple. In other respects, her age, sex, and history, she was a typical case of the latter disease. The association of abdominal pain of no discoverable cause has been described in other patients; this was also a feature of the following case:

Case II. Mrs. D., a patient of Dr. Arnold W. Stott, aged 74, complained of pain in the left side of the abdomen since an accident in August 1922. In the following month cyanosis appeared, and persisted, varying in degree from day to day. There was no associated dyspnoea. She was very constipated, and the stools were said to be unduly offensive. On examination in November 1922 she was cyanosed, the lips, gums, and tongue being of a slaty-blue colour. No other abnormal physical signs were found. A blood-count (19.12.22) yielded the following result:

Red blood-cells	4,500,000 per cmm.
Haemoglobin	70 per cent.
White blood-cells	10,400 per c.mm.
Differential leucocyte count:	
Polymorphonuclears	72 per cent.
Eosinophils	4 " "
Lymphocytes	18 " "
Large mononuclears	6 " "

Spectroscopic examination of the blood showed the typical bands of sulphaemoglobin, unaffected by the addition of ammonium sulphide.

She was treated by the administration of purges and kaolin, and by dietetic changes, including restriction to a milk diet. In March 1923, when cyanosis was still present in much the same degree as before, the stools were examined, and a considerable growth of the nitroso-bacillus was obtained. An autogenous vaccine was prepared, and two series of doses administered; the first of these, the maximum dose of which was 1,000 millions, appeared to produce an improvement; doses up to 20,000 millions were then given, and during the administration of these the cyanosis disappeared, and has not since recurred. No other method of treatment that had not previously been tried was instituted during this period. The patient has now been free of symptoms for over a year, and is in remarkably good health for her age. The latter, indeed, is the most striking feature of her case; no case of sulphaemoglobinaemia at so advanced an age as this has hitherto been recorded.

Investigations since Recovery.

In both these cases recent bacteriological examinations of the faeces have been made, the same technique as before being employed. No growth of the nitroso-bacillus was obtained in either case.

The blood-serum of each patient has also been examined for evidence of immunity to this organism, agglutination and complement-fixation tests being carried out. When the original growth of the nitroso-bacillus was obtained from Case I, both these tests had been applied with completely negative results. The following results were obtained from agglutination tests :

Serum.	Emulsion.	Dilutions.					
		1 in 25	50	100	250	500	1250
Case I	Nitroso-bac., Case I (S. S.)	+	+	+	+	+	-
Case I	" " (B. C.)	+	+	+	-	-	-
Normal human	" " (S. S.)	-	-	-	-	-	-
Normal human	" " (B. C.)	-	-	-	-	-	-
Case I	" " II (B. C.)	+	+	+	+	+	-
Case II	" " (S. S.)	+	+	+	-	-	-
Case II	" " (B. C.)	+	+	-	-	-	-
Normal human	" " (S. S.)	-	-	-	-	-	-
Normal human	" " (B. C.)	-	-	-	-	-	-
Case II	" " I (B. C.)	+	+	+	-	-	-

'S. S.' = Saline suspension.

'B. C.' = Broth culture.

From these data it is evident that agglutinins exist in the serum of both patients, not only for the nitroso-bacillus originally cultivated from their own faeces, but in each case for that obtained from the other. In all probability the two organisms are identical; separate living cultures had, however, been maintained, which enabled tests with homologous bacilli to be carried out.

The complement-fixation test, which had also been negative in Case I before treatment was begun, was performed again in both cases, the antigen used being a saline suspension of the organism, of a strength of 1,000 million per c.c. These tests were kindly carried out by Dr. H. E. Archer. In both cases a positive result was obtained.

From these facts it may be concluded that the patients had been immunized, at all events to a considerable extent, by the large doses of vaccine employed.

Cultural technique employed. A special method was used for the examination of the stools in these cases, without which the same result might perhaps not have been obtained. This method, which had been devised for other purposes, consisted in completely emulsifying a weighed amount of stool in sterile water, and making a series of measured dilutions from this emulsion, from each of which 0.1 c.c. was sown on to thoroughly dried litmus-lactose-agar plates, and spread for at least 30 seconds, during which time complete absorption of the fluid by the surface of the medium took place. Three such series of plates were sown, there being six in each series, the amount of stool contained in each culture ranging from 1/50,000th to 1/10,000,000th of a gramme. These were incubated at 37° C., 30° C., and 20° C. In those incubated at 37°, only colonies of coliform bacilli and streptococci were obtained; in the other two series the colonies of coliform bacilli were much smaller, and on the fourth day colonies of the nitroso-bacillus appeared.

Four factors seem accountable for obtaining this growth. Sowing a long series of plates from measured dilutions ensures, in the first place, that one or two

shall contain what may be called an optimum number of colonies: it was found in the course of similar work that stools may contain anything between less than one million and over one thousand million living organisms per gramme, and since the probable amount of growth cannot be estimated to any reliable extent beforehand, it is obvious that such a method as this must be necessary to ensure ideal results. In the second place, complete emulsification (by means of a powerful syringe) ensures that no clumps of organisms shall be sown, and thorough spreading results in uniform spacing of single organisms, and consequently of the resulting colonies. Thirdly, the unusually prolonged drying of the plates (at least 5 per cent. of the water in the medium being evaporated before sowing) not only ensures absorption of the inoculate and therefore discrete colonies, but, to some extent, limits the size of these colonies, however long incubation may be continued. Lastly, incubation at temperatures of 30° and 20° C. further limits the size of indifferent colonies, such as those of *B. coli*, while providing a condition favourable to the growth of the nitroso-bacillus. The effect common to all these factors is to provide the organism with room to grow; their neglect must result in overgrowth of the plates by *B. coli* during the prolonged incubation which must elapse before colonies of the nitroso-bacillus become visible.

The growth obtained in Case I was profuse, the colonies of the nitroso-bacillus greatly outnumbering those of all other organisms. In Case II they comprised about 40 per cent. of the colonies obtained by incubation at 20°. This method of culture was applied to a large number of stools from other patients, all suspicious colonies being sub-cultivated and tested, but in no case was the nitroso-bacillus recovered from the stools of patients suffering from other diseases, or from those of normal persons.

The characters of the organism in each case were almost identical with those described by Mackenzie Wallis. It was an oval, Gram-negative, non-motile bacillus, growing slowly on all media, fermenting no sugars, reducing neutral red, liquefying gelatin, and forming nitrites. It differed, however, in this particular, that growth occurred at 37° C.: the temperature of incubation, between the limits of 20° and 37° C., appeared to be indifferent, the size of the colonies and the time of their appearance being much the same in either case. This was observed in subcultures only, incubation at lower temperatures being necessary, for reasons already stated, in order to obtain the original growth. It is to be expected that an organism infecting the human subject shall be capable of normal growth at body temperature, and this observation is therefore much more in accordance with the hypothesis of Mackenzie Wallis in regard to the causation of the disease than his own findings as to the properties of the organism in this particular.

In order to determine whether nitrite production is peculiar to this organism, at least among bacilli present in material from human sources, broth subcultures of numerous Gram-negative bacilli from a variety of specimens were tested with Ilosvay's reagent; no other organism producing nitrites was found.

Further observations were also made with the object of determining whether

the nitroso-bacillus is capable of producing sulphuretted hydrogen. It was sown into tubes containing sterile haemoglobin solution, to which were added various amounts of an alkaline solution of cystin, and, in another series, ammonium sulphate (0.25 per cent. and 1 per cent.). These, with uninoculated controls, were incubated at 20° and 37° C. The cultures were examined spectroscopically after five days' incubation, and sulphaemoglobin was not found. This accords with Mackenzie Wallis's observation (made with cultures which did not contain haemoglobin) that the nitroso-bacillus does not generate sulphuretted hydrogen, even in destroying cystin.

It is also, in a negative sense, in accordance with the hypothesis which accords to the organism the role of forming a reducing substance only. The same may be said of the original results of the agglutination and complement-fixation tests. The role attributed to the organism is that of a saprophyte; it neither invades the tissues nor generates a toxin, and would therefore not be expected to excite antibody-formation. If, however, immunity be excited artificially by the administration of a vaccine, a consequent inhibition of its growth might then be expected to follow. That anti-bacterial substances were produced in the blood during treatment is demonstrated by the clearly positive results obtained after recovery with both the above tests.

The doses of vaccine used in these two cases were larger by far than those employed by Mackenzie Wallis, and the fact that undue reactions were not produced (nothing beyond slight local swelling and a few hours' malaise following the largest doses in either case) may be accounted for by the fact that the organism contains no toxin, and is, in fact, no more poisonous when injected subcutaneously than would be any emulsion of an entirely non-pathogenic organism. It may be observed here that there is no other known example of an infection whose sole action on the body is exerted, not by a toxin, in the proper sense of that term, but through the agency of a product the effects of which are due to a single known chemical property.

Reference must finally be made to the recent work of van den Bergh and Wieringa, which at first sight appears to invalidate the conception of sulphaemoglobinaemia with which this paper is concerned. In the original experiments of Wood Clarke and Hurtley, the alleged reducing agent which was found most readily to favour the production of sulphaemoglobin in solutions of haemoglobin with sulphuretted hydrogen was phenylhydrazin. Van den Bergh has found that this accelerated change takes place only when oxygen is present, and further, that no combination at all of sulphuretted hydrogen with either haemoglobin or reduced haemoglobin can take place if oxygen be completely excluded. Further, he estimated the effect on this combination of other reducing agents, and found that the rapidity of sulphaemoglobin formation was by no means proportional to their reducing power, some, indeed, having no effect whatever. He concluded, therefore, that the action of phenylhydrazin in Wood Clark and Hurtley's experiment was not that of a reducing agent, but that of an 'activator of oxygen'.

The superficial implication, from the point of view of Mackenzie Wallis's hypothesis, is that the existence of a reducing agent in the blood-serum in sulphaemoglobinaemia is of no consequence in attempting an explanation of the disease. The actual effect, however, of these observations is rather to complicate the question than to necessitate a new line of approach. The substance found in the serum in sulphaemoglobinaemia, and in cultures of the nitroso-bacillus, is indeed a reducing agent, but its chemical composition is unknown: it may share with phenylhydrazin the power of 'activating oxygen', if that is the true mode of action of phenylhydrazin; it may, indeed, be phenylhydrazin itself, or a substance very closely related to it. The existence of a foreign substance in the blood which favours the combination of haemoglobin with sulphuretted hydrogen remains the only plausible explanation of this disease which has been put forward. The fact that sulphaemoglobin is not formed in the blood even in poisoning by sulphuretted hydrogen, when a gross excess of the latter is present in the body, suggests strongly that the action of some intermediary substance is essential.

These observations are therefore put forward with no sort of claim to finality. There is still much that remains obscure in the mechanism of this disease, and its difficulties are likely to persist until the conditions governing the formation of sulphaemoglobin are better understood. It does, however, appear desirable to claim again for the nitroso-bacillus, and for the hypothesis connected with its discovery, the advantage of full investigation in such cases of sulphaemoglobinaemia as may present themselves. There is no other hypothesis as to the origin of this disease which attempts to explain all the facts known with regard to it, or, indeed, which offers any reasoned suggestion at all as to its aetiology. In appealing for such investigation, it may be pointed out that search for the nitroso-bacillus is simplified by the altogether peculiar characters of this organism. Were it a member of the coli-typhoid group, distinguished solely by certain sugar reactions or agglutinogenic properties, the identity of any given example might well remain in doubt, and its discovery in cases of sulphaemoglobinaemia might well be dismissed as of no significance. Its properties, however, are such as to distinguish it sharply from any other organism hitherto described as inhabiting the human body, and a deliberate search has failed to disclose the existence of an organism with which it may be confused.

Conclusions.

In two cases of sulphaemoglobinaemia the nitroso-bacillus was obtained in culture from the stools.

Examination by the same technique of stools from cases of other disease failed to reveal its presence.

Recovery in the two cases took place during the administration in large doses of a vaccine prepared from this organism.

After recovery, no growth of the nitroso-bacillus could be obtained from the stools, and immune substances to this organism were found in the blood-serum of both patients.

I am indebted to Dr. Morley Fletcher and Dr. Stott and to both patients for permission to record their cases, and to Dr. Mackenzie Wallis and Dr. Gordon for valuable help.

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THE CLINICAL ASPECT OF BUNDLE BRANCH BLOCK¹

By JOHN COWAN AND J. CRIGHTON BRAMWELL.

With Plates 12-16

I. *The Electrocardiogram of Bundle Branch Block.*

THE introduction of the electro-cardiograph into practical medicine is producing a profound impression upon our knowledge of the myocardium. So long as we had to depend upon our ears and upon our fingers for physical signs, the myocardium was relatively a 'silent area'. But now we can demonstrate in the clinic, as accurately as in the laboratory, not only the gross changes in rhythm such as extra-systoles, fibrillation, and heart block, but also the much more elusive perversions of function indicative of pathological changes within the ventricles. The data which have been accumulated have already led to greater accuracy in the prognosis and in the treatment of cardiac affections, and there is good reason to hope that the practical application of this new knowledge will yield even greater benefit for our patients when the available facts have been more thoroughly assimilated.

Bundle branch block was first described in 1910 by Eppinger and Rothberger (1). Their observations have been expanded and corroborated by Rothberger and Winterberg (7), and by Lewis (4); but the number of cases recorded *clinically* is still limited. A series of twenty-four cases which we have seen in hospital and in private practice drew our attention to this disorder, and in this paper we have attempted to analyse from the clinical aspect the information afforded by these cases.

The characteristic electro-cardiogram of bundle branch block (Pls. 12 and 13, Figs. 5, 6, 7) is very striking. The ventricular complex is wholly abnormal. The Q.R.S. group is represented by a single large deflexion which often shows a notch at its apex, or a thickening of one or the other limb. The total duration of this deflexion exceeds 0.1 sec., its two limbs being widely separated from one another. The T-wave is directed in the opposite direction to the initial deflexion, and is often of large amplitude and of increased duration (Pls. 12 and 14, Figs. 6, 9). Thus, in Leads I and III, and sometimes also in Lead II, there are only two prominent deflexions instead of the usual three or four. The complex is diphasic.

¹ Received August 23, 1925.

Either branch of the bundle may be affected, but the right is much more frequently involved than the left. If the right branch be concerned, the first deflexion in Lead I is directed upward and the second downward (Pl. 12, Fig. 6), while in Lead III the first wave is directed downward and the second upward. In left branch block the first deflexion in Lead I is directed downward and the second upward (Pl. 12, Fig. 4), and vice versa in Lead III. Thus in right branch block the ventricular complex is similar to that of recurring extra-systoles arising in the left ventricle; while in left branch block it resembles that of recurring extra-systoles arising in the right ventricle. The reason for this similarity is obvious, for, if one branch of the bundle be functionally defective, a stimulus can only reach the corresponding ventricle by passing down the opposite branch, and then leaving the Purkinje tissue and crossing over through the unspecialized muscle fibres. Hence the duration of the initial phase of the ventricular complex is necessarily prolonged.

It is not uncommon to meet with electro-cardiograms which in certain respects resemble those of bundle branch block, but fail to comply with all the requirements of typical records. Although such cases are in all probability examples of bundle branch block in an incomplete form, we have decided not to include them in the series recorded in this paper; for, in the present state of our knowledge, it seems advisable to confine our attention to cases which yield absolutely typical records. The number of cases is in consequence small, but seems sufficient to give some indication of the conditions with which this defect is liable to be associated, and of the prognostic significance which is to be attached to its presence.

II. *Analysis of Cases.*

(a) *Incidence.* In all but one (Case XIV) of the twenty-four cases in our series, the block involved the right branch of the bundle. In two cases (Cases III and V) electro-cardiograms were obtained prior to the development of bundle branch block; but we have only met with a single exception (Case XVI) to the rule that the condition, once established, tends to be permanent.

Four of our patients were women; twenty were men.

Their ages (Fig. 1) ranged from twenty-three to seventy-three, and all but three were over forty years of age, five being in the fifth, seven in the sixth, eight in the seventh, and one in the eighth decade. The condition is thus most commonly found in the degenerate period of life.

(b) *Mode of onset.* It is difficult to determine with certainty the mode of onset, for there are no signs, save the electro-cardiogram, which can establish the diagnosis. In the majority of cases, however, it seems to be insidious. One patient (Case III), who was in the wards for a lengthy period, showed full heart-block without bundle branch block (Pl. 16, Fig. 12 a) on July 4, 1919, while the electro-cardiogram (Pl. 16, Fig. 12 b) of October 18, 1919, showed full block and bundle branch block. He was an old man who suffered from Adams-Stokes seizures,

and his general symptoms were those of progressive cardiac failure, but during this period he had no dramatic attack, and the exact date of onset of the bundle branch block cannot, in consequence, be appreciated. In some instances, however, the onset is apparently abrupt. Case V, for example, came under observation on January 11, 1922. The electro-cardiogram (Pl. 14, Fig. 14 a) at that time showed no block. Subsequently he went to the south of France, and, on his way home in the train, took ill very suddenly with symptoms indicative of cardiac weakness. It was not expected that he would recover; but, after a few days, improvement ensued, and he was able to return home. An electro-cardiogram (Pl. 14, Fig. 14 b) on December 21, 1922, showed right bundle branch block, which seems most probably to have occurred at the time of his sudden seizure.

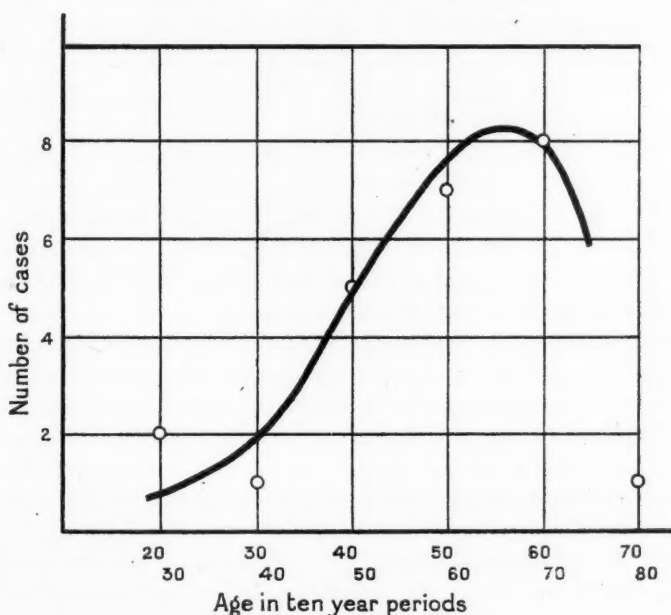


FIG. 1. Age incidence in 24 reported cases.

Whether in cases of heart failure, with oedema and congestion of the internal organs, bundle branch block is merely a terminal event our data do not enable us to say, as it is only in two of our cases (Cases III and V) that we have electro-cardiograms prior to the development of the bundle branch lesion. On the other hand, in Case XVI (Pl. 16, Fig. 13), bundle branch block was known to be present for five months and subsequently showed a tendency to disappear; the change in the electro-cardiogram coinciding with a marked improvement in the clinical picture. Lewis (5), Ritchie (6), and Hewlett (3) have recorded similar cases in which bundle branch block was present as a temporary manifestation in association with some febrile or toxic disturbance.

(c) *Symptoms.* In the majority of our patients the principal complaint has

been either shortness of breath (13 cases) or anginal pain (8 cases), but oedema, palpitation, faintness, and convulsions have, in some instances, been prominent features. The symptoms are thus in no way characteristic, and are merely the expression of cardiac insufficiency such as may be seen in other types of heart disease.

(d) *Associated cardio-vascular conditions.* Cardiac enlargement was extreme in six cases, less pronounced in eight, and slight or absent in the remaining eleven cases. There was evidence of chronic valvular disease in ten cases. Of these, three (Cases XIV, XV, XXIV) had old-standing mitral stenosis, associated with auricular fibrillation and an advanced degree of congestive heart failure. The aortic valve alone was affected in two cases (Cases VI and XVI). There was mitral incompetence in one case (Case XIII), while in three cases (Cases II, VIII, and X) both aortic and mitral valves were incompetent. In Case II the valvular lesion was associated with great cardiac enlargement, congestive heart failure, and auricular fibrillation. In two cases (Cases XII and XVIII) there was evidence suggestive of a congenital lesion.

In five cases in our series the electro-cardiogram showed auricular fibrillation. One of these patients (Case XX) was admitted to hospital with a transient hemiplegia and aphasia which rapidly cleared up. His heart was not much enlarged, and there was no evidence of any valvular lesion. The other four cases in which fibrillation was present all exhibited old-standing valvular lesions, and have been referred to in the preceding paragraph.

In Case III the bundle branch block supervened on a condition of complete a.-v. block. The remaining eighteen cases exhibited normal sinus rhythm. Ventricular extra-systoles² occurred occasionally in ten cases, while in Case XII at times they were so frequent as to give rise to long spells of bigeminal heart action (Pl. 15, Fig. 11).

Palpable thickening of the superficial arteries was noted in five cases.

The systolic blood-pressure was under 150 mm. Hg in ten cases, between 150 and 200 in eight cases, and over 200 in two cases. It was not noted in the remaining four cases. Six of the patients had had rheumatic fever, and in two there was evidence of previous syphilis.

From these figures it is evident that in our series of cases there is no constant association of bundle branch block with any disease of the valves, or with any abnormality of rhythm.

The common factor is clearly myocardial. Evidence of degenerative changes in the arterial system is common, with or without hypertension, and is sometimes accompanied by chronic nephritis.

² In addition to simple extra-systoles, in several cases (see Pl. 13, Figs. 7, 8) occasional ventricular complexes have been noted, which differ markedly in form from those which are 'normal' for the particular patient. Such complexes are not necessarily premature, and may be less strikingly aberrant than those in the remainder of the record. Their appearance suggests that under certain circumstances conduction through the affected branch may temporarily be partially restored, but to discuss their significance is beyond the scope of this paper.

III. Discussion.

(a) *Diagnosis.* There is no clinical sign of bundle branch block save the electro-cardiogram. One might imagine that a doubled first sound would be present, but it was only noted in a small proportion of the cases in this series. It may occur, too, in the absence of this defect, for in a recent case in which the sign was well marked the electro-cardiogram failed to show bundle branch block, or indeed any probable cause of the doubling. A 'wavy' apex impulse, too, was not associated with this abnormality.

(b) *Prognosis.* One is not astonished to find that the patients with bundle branch block manifest cardiac symptoms, as the block is an indication of myocardial disease. But it is surprising that in some cases there is so little interference with the patient's activities. Case V, for example, carried on the duties of a busy parish for more than two years after the block was detected, and ultimately died, not from his heart, but from cerebral haemorrhage. Case VI, a shopkeeper, is still at regular work, though his block was found more than two years ago. The old lady of 65 (Case VIII) is now in better health than she was a year ago, though the block persists. Case IX, who has had bundle branch block for three years, is really suffering from 'heart on the brain' and is more neurasthenic than cardiac. Case XVI has been able to follow his employment as a japanner for three years, and his most recent electro-cardiogram (Pl. 16, Fig. 13 b) shows a tendency for the ventricular complex to revert to the normal form. Case XVII has now been under observation for a period of nearly three years, during which time he has experienced no difficulty in carrying on the by no means sedentary occupation of a postman.

The important factor in prognosis is not the block itself, but the pathological lesion which causes the block. If that lesion be localized and stationary, the outlook is favourable; but if it be only part of a widespread degenerative process, affecting not only the myocardium but also other organs, the prognosis is grave. A bundle branch lesion should not be regarded as a definite pathological entity, but rather as a significant feature in the general picture of myocardial damage.

The duration of life subsequent to the electro-cardiographic finding of bundle branch block is shown in Fig. 2. Ten of our patients are still living, fourteen have died. Of the ten surviving cases one has now been under observation for over four years, two others for over three years, two for over two years, three for over one year, and the remaining two for a period of less than one year.

In none of these cases were there any objective signs of cardiac insufficiency, although in two (Cases IV and VI) the heart was considerably enlarged, and in one (Case XX) there was auricular fibrillation.

Of the fourteen fatal cases, only one (Case V) lived for more than two years subsequently to the recognition of bundle branch block, and he died, not of heart failure, but of cerebral haemorrhage. Another patient (Case VII),

who survived sixteen months, eventually died of bulbar paralysis. Of the remaining twelve fatal cases, two survived for one year, four for a period of less than a year, and six died within one month of the detection of the bundle branch lesion.

The actual cause of death was uraemia in two cases, influenza in one, acute heart attacks in two, and progressive heart failure with congestion in the remaining seven cases. Of the seven patients who died of heart failure, four were *in extremis* with great cardiac dilatation and auricular fibrillation, and the other three all manifested gross signs of cardiac insufficiency at the time they first came under observation.

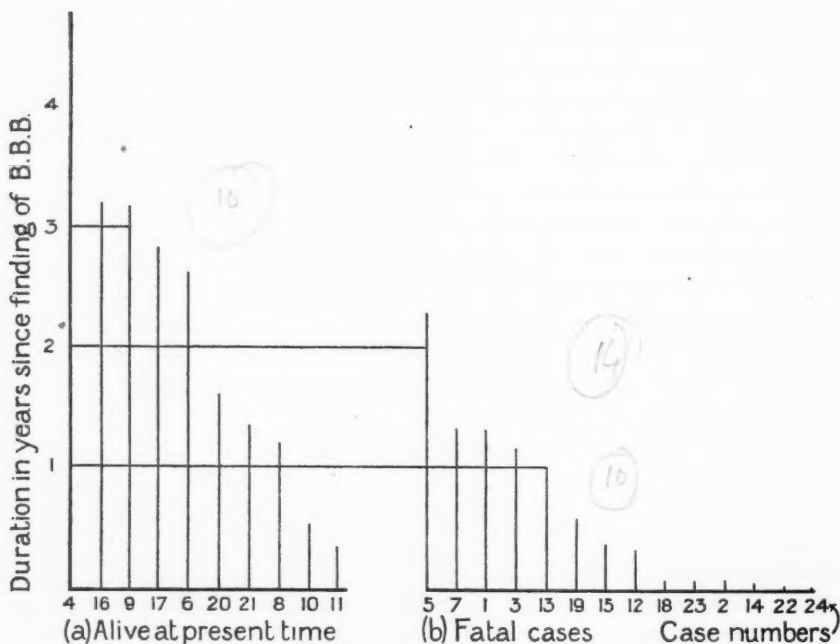


FIG. 2. Diagram to show duration of life in each case subsequent to recognition of B. B. B.

While we fully realize that the number of cases we have seen is too small, and that the period during which they have been under observation is too short, to enable us to appreciate the full prognostic significance of this condition, there are two conclusions which appear to be justified by our observations: namely that, whereas the association of bundle branch block with signs of cardiac insufficiency is of extremely grave significance, the condition by itself, in the absence of other serious manifestations, may be quite compatible with a fairly active life.

(c) *The causes of bundle branch block.* In cases of bundle branch block which have come to post-mortem the branch has generally been found to be

involved in fibrous tissue. In full heart-block a similar origin is the most common, though gumma, tumour, infarct, and an inflammatory myocarditis have also been recorded. It seems probable that fibrosis will be found to be the most common cause of bundle branch block.

Fibrosis of the heart may occur from several causes. In the large majority of cases it is the sequel of degeneration of the muscle cells and is therefore a secondary fibrosis, the muscle degeneration being due to interference with the coronary blood supply. Less frequently the fibrosis is the result of connective tissue overgrowth following infective lesions in the heart or other organs. Fibrosis may be due to mural endocarditis. From the pathological side, therefore, arterial disease seems most likely to be the cause of bundle branch block, though inflammatory lesions and gumma may account for a few cases.

The records which are available point in the same direction. So far as is known, only two of our patients had had syphilis, and six rheumatic fever. Five patients showed definite evidence of arterial disease in the superficial vessels, and eleven patients had a blood-pressure above 150 mm. Hg, a height which is pathological, and extremely likely to be accompanied by disease of the arterial tree.

In Case VI the close connexion of an attack of rheumatic fever, accompanied by aortic valvular disease, suggests an inflammatory origin of the block.

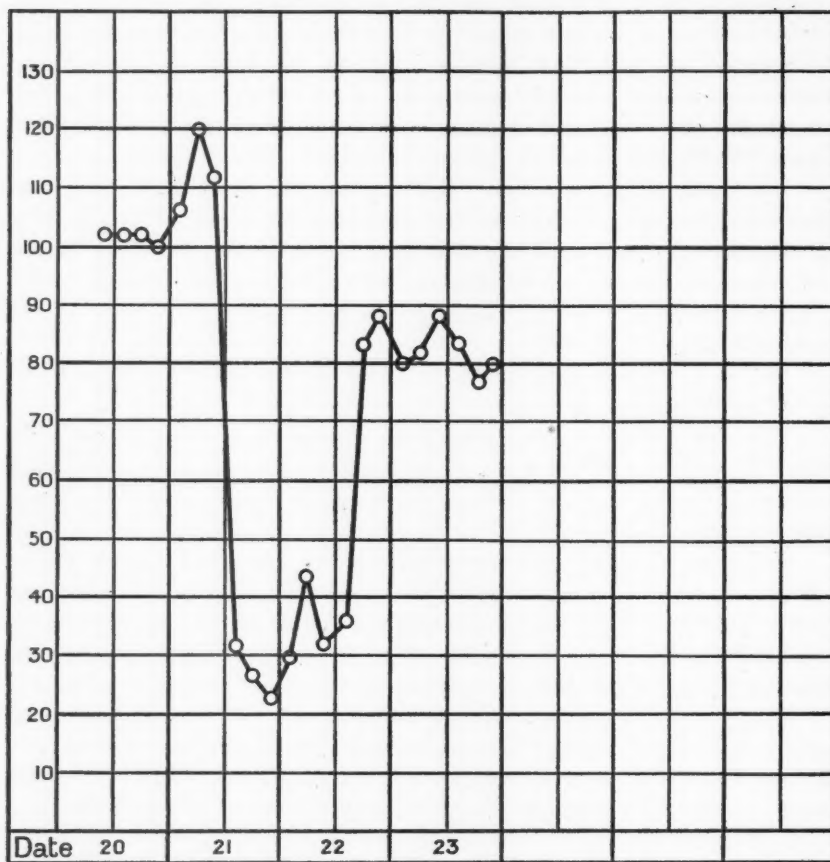
The abrupt onset of serious cardiac symptoms in Case 5 suggests the possibility of infarct as the cause, or an intramuscular haemorrhage, as he had suffered previously from cerebral haemorrhage, and subsequently died from another seizure.

Full heart-block may occur suddenly, as in the following instance: A man, aged 47, was admitted into hospital on account of pains in his chest and shortness of breath which had succeeded a 'cold'. He had well-marked double aortic valvular disease, the result of an attack of rheumatic fever twenty-six years previously, and he had been in hospital on account of symptoms of cardiac insufficiency on two occasions. At 3.40 o'clock on the afternoon succeeding his admission he had an epileptiform attack which lasted for about five minutes. His pulse-rate (Fig. 3) was now found to be 32, though it had numbered 112 at noon. It subsequently fell to 22, and it remained infrequent until 4 o'clock on the next afternoon, when it was found to number 84. His subsequent progress was good. No tracing was taken prior to his seizure, but after the convulsion had occurred the electro-cardiogram showed full heart-block, the auricles beating at about three times the rate of the ventricles. Next morning the block was still complete, but on the next day the rhythm was found to be normal, with a P.-R. interval of 0.32 seconds. A week later the P.-R. interval measured 0.20 seconds, and a week later 0.14 seconds. The duration of the full block was thus almost exactly 24 hours. (No digitalis had been given in this case.)

In full heart-block the sudden onset is shown *clinically* by characteristic symptoms. But as branch bundle block does not produce any distinctive symptoms, its onset can only be suspected by the occurrence of symptoms of

muscle failure. If these appear suddenly and block is discovered later on, an acute onset of the block may reasonably be diagnosed.

In cases with a gradual onset, a progressive narrowing of arteries, or a progressive fibrosis, seems the probable cause; while haemorrhage or blocking of a vessel would account for a sudden onset. Comparable lesions have been found affecting the main bundle in cases of full heart-block.



Date of admission 20.vi.23

FIG. 3. Pulse chart, in case of transient full heart-block described on p. 101.

In three cases recorded in the literature the block was temporary. In Lewis's case block was found during a febrile attack, and had gone next day. In Ritchie's case the patient was at the time showing signs of jaundice. In Hewlett's case the patient was suffering from urinary sepsis; with improvement following operation the block disappeared. In one of our cases (Case XVI) the ventricular complex of the electro-cardiogram shows a tendency to revert to the normal form.

Temporary incomplete full heart-block is relatively common, and many instances are on record. It is most common in rheumatic fever, but has occurred in gonococcic infections, influenza, enteric fever, pneumonia, &c. In cases with full heart-block which have come to section, inflammatory lesions have been found in the region of the bundle, and comparable lesions of lesser degree are presumably the cause in the cases which recover. But as heart-block may be produced by such drugs as digitalis, aconitine, muscarine, &c., toxic causes may presumably originate a temporary block, without any gross cellular changes in the connective tissues.

Smith's (8) experimental data, however, complicate the matter, for he has not yet seen the characteristic electro-cardiogram of bundle branch block in animals with occluded coronary arteries. The reason of this unexpected result is probably the fullness of the vascular anastomoses. Gross (2) states that the anastomoses are numerous. They exist between the capillary and the pre-capillary branches of the two main arteries, between the branches of each coronary artery, and between branches of the coronary arteries and those of the adjoining organs. One part of the heart may be damaged by ischaemia, and the tissue in its immediate vicinity intact. A normal bundle has been found in the midst of scar tissue, and the bundle may show scars without the surrounding tissue being affected.

The superficial position of the bundle branches, too, may account for their preservation in cases where the underlying myocardium is damaged. For, as Muir long ago pointed out, the muscle-cells underlying the endocardium generally escape destruction in those cases which show loss of the more central cells presumably as the result of their close connexion with the intracardiac blood.

It is unlikely that bundle branch block is often the result of mural endocarditis, for this is most common on the left side of the heart, while branch bundle block is most common on the right side. We have, however, specimens of mural endocarditis on the right side, but all of them prior to the advent of the electro-cardiograph. But endocarditis of the mitral and of the aortic valves is frequently accompanied by a spread of the inflammation into the central area of the heart, with resultant heart-block. A slight variation in the direction of the spread would involve the branches instead of the bundle itself.

In our series the right branch of the bundle was involved in twenty-three cases, the left branch in but one. It is difficult to find an entirely satisfactory explanation. There are, however, differences in the blood-supply to the two branches which may account for this discrepancy. Much of the conducting tissue has a specific blood-supply of its own. Gross states that the a-v. node is generally supplied by a constant branch of its own, which generally arises from the right coronary artery. The right branch of the bundle may have its upper part supplied by the artery of the node, but its main supply comes from a specific artery which arises from the descending branch of the left coronary

artery. It is well known that this branch (of the main artery) is more frequently degenerate than any other of the cardiac arteries.

The left branch of the bundle, on the other hand, has no specific blood-supply of its own, and receives its blood from the vessels which nourish the underlying myocardium. Both coronary arteries are here concerned, the right artery supplying the posterior part of the bundle branch, and the left artery the anterior part of the bundle branch. If one artery is narrowed, the anastomotic developments of the other may be able to compensate the fault and prevent structural, or even functional, disturbance.

The form of the bundle branches may make the right more vulnerable than the left. The right is a slender strand, readily destroyed by even a tiny lesion. The left branch is a broad tape, spread over an area of considerable size, which would only be partly damaged by a lesion large enough to destroy the right one completely.

The frequency with which the right branch of the bundle is involved as contrasted with the left is thus most probably due to the difference in the size of the two branches, and to the fact that, while the right branch is supplied by a specific artery arising from the left coronary artery, the left branch is supplied by many vessels which arise from both of the coronary arteries.

Case Summaries.

Case I. A short stout man aged 53, a clerk by occupation, who had had rheumatic fever 15 years previously, became short of breath after an attack of bronchitis in the spring of 1915. In the autumn his heart was considerably enlarged, but the sounds were pure. The blood-pressure was 190/165. The urine was normal. A few râles were audible at the bases of the lungs, but there was no oedema, and the liver was not enlarged.

After six weeks' rest he resumed work, though he was still short of breath on exertion. Sixteen months later, however, he suddenly became extremely short of breath, his pulse became very frequent and irregular, and he died within a few hours.

Case II. A sawyer, aged 47, had been short of breath for three years, but had been able to carry on his work till a year before his admission to hospital. He had had three attacks of rheumatic fever the last twelve years previously. A well-developed man who had evidently lost weight, he was orthopnoeic and oedematous, his liver was large and tender, and râles were present at the bases of the lungs. The urine contained albumin in quantity. The heart was greatly enlarged. The aortic and mitral valves were incompetent. Electro-cardiograms showed the presence of auricular fibrillation and right branch bundle block. The Wassermann test was negative.

For a fortnight after his admission he made good progress, but then, without obvious cause, his symptoms returned and increased in severity, and he died a week later. His heart dilated still further before death.

Case III. A retired shoemaker, aged 73, who had ceased work five years previously. He had contracted syphilis at the age of 46, but his treatment had been thorough and apparently efficient, for the Wassermann test was negative at the time of observation. His health had been good till nine months before admission to hospital, when he noticed that he was becoming short of breath

upon exertion. Six months later he became sleepless and subject to minor Adams-Stokes seizures, and felt pains in his head and left arm.

He was a big, well-developed man, but looked old and frail. There were râles at the bases of the lungs, but no oedema. The heart was considerably enlarged, but the sounds were pure. The arteries were notably hard and tortuous. The blood-pressure was 190/140 mm. Hg. Electro-cardiograms showed full heart-block with a ventricular rate of 32-48.

During the early weeks of his residence, numerous slight Adams-Stokes attacks were recorded. In the early autumn the attacks were less frequent, and the pulse-rate sometimes rose to 70, though it was usually about 35. But it was clear that the heart was failing, for oedema made its appearance in the legs and steadily extended upwards, and the râles at the bases were more numerous. Four months after his admission the electro-cardiogram (Pl. 16, Fig. 12 *b*) showed, as before, full heart-block, *with in addition* right bundle branch block. The subsequent progress was slowly but steadily downhill, and he died eighteen months after his admission to hospital.

Case IV. A professional man, aged 60, who had had many illnesses in the past, and in whom albuminuria and a high blood-pressure had been known to obtain for some four or five years, was suddenly awakened from sleep one night with great shortness of breath and oppression in the chest. This, however, rapidly passed off, but it recurred two nights later.

He was a short man of ruddy complexion, and distinctly fat. His heart was much enlarged. The sounds were pure but short. The arteries were thickened. The blood-pressure was 200-120 mm. Hg. He is alive, in poor health, four years after the recognition of the bundle branch lesion.

Case V. A Padre, a stout man aged 57, of active and energetic habits, who had served in France for three years during the war, experienced pain in the left side when walking, in the summer of 1921. In January 1922 his right hand and arm felt numb, but his symptoms were entirely subjective. At this time his heart did not appear to be large, the sounds were pure, but the blood-pressure was 250/135 mm. Hg. His arteries did not appear to be notably thickened. The urine was of low specific gravity and contained a small amount of albumin.

Under treatment he made considerable progress, but when in the train, while returning from the south of France, he suddenly took very ill with symptoms of cardiac failure, and was thought to be dying. After a few days, however, he began to recover, and by December he felt better than he had done since the commencement of his ill health. No appreciable changes could be detected in the heart, but the electro-cardiogram (Pl. 14, Fig. 14 *b*) now showed full right bundle branch block, though at the beginning of the year no suggestion of this abnormality was present.

In 1923 and 1924 he maintained fair health and was able to continue at his work. But in March 1925 he died suddenly from cerebral haemorrhage. From the commencement of his illness to the end he had no cardiac symptoms of any note, save at the time of his serious illness in the spring of 1922.

Case VI. A nervous fellow, aged 51, of only moderate physique, had an attack of acute rheumatism in the summer of 1922. He made a fair recovery and was able to resume his work.

His heart was considerably enlarged, and double murmurs were audible all over the sternum. The blood-pressure was 165/110 mm. He had no definite signs of cardiac insufficiency. But the electro-cardiogram showed a right branch bundle block. A year later the electro-cardiogram was unchanged. At the present time, more than two years after the lesion was first detected, he remains in good health and at work.

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Case VII. A retired naval man of 69 had suffered from slight attacks of angina upon exertion six years previously. At the age of 68 the attacks returned, and in January 1923, for the first time, occurred during the night, awakening him from sleep. The diurnal attacks, too, became more frequent and more severe, and occurred on even the most trivial exertion.

His heart was large, and the blood-pressure 190/95 mm. Hg. The cardiac sounds were distant and short, and a systolic murmur was audible at the apex. The arteries were hard and tortuous. Occasional right ventricular extra-systoles were noticed.

He was kept at rest for a month, and the attacks of angina became minimal in their intensity, but his general strength rapidly failed. Cerebral symptoms soon supervened. He became stupid and irritable, and lost the power of holding his pen. As time went on, he became more frail. The weakness in the muscles of the hand increased in degree, and spread upwards to the shoulder. The blood-pressure fell to 160 mm. Bulbar symptoms ensued, and he died in July 1924, sixteen months after the bundle branch block had been first recognized.

Case VIII. A stout old lady of active habits, aged 65, had been drifting into bad health during the preceding six months. She complained of shortness of breath, and a feeling of oppression in the chest upon exertion; but she did not evince any signs of cardiac failure of the usual type.

The left heart was large, and systolic murmurs, probably of aortic and mitral origin, were audible everywhere in the cardiac area. The blood-pressure was 175/75 mm. A small haemorrhage was visible in the right fundus. With commonsense restrictions and care her health steadily improved. Ten months after the bundle branch block had been detected she was very well, and able to perform her usual duties quite comfortably, though she became short of breath and had discomfort if she attempted to do too much. The bundle branch block has persisted unchanged.

Case IX. A crane-man, aged 47, who had suffered from subacute pains of anginous type on exertion for some six years, had a severe attack of pain one evening. The pain persisted for three days, and after forty-eight hours suddenly became accompanied by extreme breathlessness. Subsequently the attacks became more frequent, and were now always accompanied by breathlessness. They were, however, of short duration, and only lasted for about fifteen minutes.

While under observation in hospital he remained free from any serious discomfort. The heart was normal in size, the sounds were pure but faint and indistinct, and the blood-pressure was low—110/70. The pulse was infrequent, and at times irregular from the occurrence of nodal and ventricular extra-systoles.

He was a well-built man of good nutrition, but very nervous and introspective, and it was very difficult to determine his real discomforts. He is still alive and in fair health, three years after the finding of the bundle branch lesion, though he considers he is quite incapable of any form of work, but his symptoms are more neurasthenic than cardiac.

Case X. The patient was a hyperactive business man, aged 54, who, a year previously, while travelling in a train, had had a convulsion without apparent cause. Since then he had had about six convulsions. These were liable to occur at any time, and appeared to be epileptic in nature, though it was not possible definitely to exclude Adams-Stokes attacks. His sole complaint, however, was that he was not sleeping well.

The apex impulse was large and well sustained and not notably displaced. Murmurs indicative of double aortic disease and also of mitral incompetence were present, but the second aortic sound was distinct, and the pulse was not notably shotty. The systolic blood-pressure was 170 mm. Hg. It seemed

probable that the aorta was at any rate dilated, if not actually aneurysmal. The arteries were not grossly hardened. It seemed probable that he had had syphilis. He is still at work.

Case XI. A professional man, aged 58, a well-built muscular fellow, who had had dysentery and malaria during the war, on his return home found that he was easily tired, and short of breath upon exertion. The onset of these symptoms had been quite insidious, but they had gradually increased in severity.

There were no signs of cardiac insufficiency of the common type, the chest being clear, the liver small, and oedema being absent. The heart was slightly enlarged. The first sounds were short, distant, and weak, and their termination was everywhere impure, though no definite murmur was detected. The second sound was accentuated and intoned. The blood-pressure was 160/105 mm. Hg. The arteries did not seem to be grossly thickened.

The electro-cardiogram (Pl. 12, Fig. 6) showing bundle branch block in this patient was obtained five months ago. He is still carrying on his work as actively as usual, and is, he thinks, in better health in every way.

Case XII. A shopkeeper, 48 years of age, a man of poor physique and distinctly cyanosed, came to the Out-patient Department in December 1920, complaining of a constant dull aching pain in the epigastrium and shortness of breath. He was said to have had heart trouble practically from birth, and had been an in-patient in a children's hospital at the age of nine, on this account.

The heart was greatly enlarged; the liver and lungs showed evidence of venous congestion; and the electro-cardiogram (Pl. 15, Figs. 10, 11) revealed right branch block.

He was admitted as an in-patient in January 1921, and remained in hospital for five weeks. At the time of admission, the heart rhythm was disturbed by frequent right-sided ventricular extra-systoles (Pl. 15, Fig. 11), amounting at times to long spells of bigeminal action. Three weeks later only occasional extra-systoles were present, and these were of the left-sided type (Pl. 15, Fig. 10). Finally these too disappeared, but the clinical condition showed little sign of improvement, and the patient died at home within a few weeks of leaving hospital.

Case XIII. A carter of good physique, aged 49, first noticed that he was short of breath when walking uphill in May 1920. In January 1921 he had to give up work, as the breathlessness had increased and was now accompanied by pain in the epigastrium. There was no history of rheumatic fever or syphilis, and the Wassermann reaction was negative.

His heart was greatly enlarged, and a systolic murmur, maximal at the apex, was audible all over the praecordium. The blood-pressure was 120/90. The percussion note over the manubrium was impaired, and X-ray examination revealed enlargement of the ascending aorta, but no definite aneurysm. The walls of the superficial arteries were thickened. The liver was considerably enlarged. There was slight engorgement of the veins of the neck, and slight oedema, and râles were present at both bases.

His symptoms were relieved by a month's residence in hospital, and in October he attempted to resume work, but was compelled to give it up a week later on account of shortness of breath and pain in the epigastrium. In December 1921 he was readmitted to hospital following an acute attack of pain and breathlessness. The location of the pain had changed somewhat. It now radiated from the region of the second dorsal spine to the left supraspinous fossa, left shoulder, and front of the chest, and spread down the posterior aspect of the left arm as far as the elbow. It was accompanied by a choking feeling in the throat.

With rest in hospital his condition again improved, and he was able to return home at the end of February.

BPT ✓

? Rheum ✓
? Long ✓

Myoc ✓

In May 1922, however, the pain became much worse, and he described it as feeling like 'a ball in the middle of the back between the shoulder-blades'. He was readmitted to hospital on June 13 with obstinate vomiting, and was expectorating a small quantity of blood-stained mucus. There was slight oedema with moderate enlargement of the liver, and the blood-pressure had fallen to 100/80. He died four days later.

Case XIV. A married woman, aged 49, was admitted to hospital on November 28, 1921. She was intensely cyanosed and dyspnoeic. Her legs were oedematous, her liver greatly enlarged, and râles were present at the bases of the lungs. The symptoms dated from a confinement in 1912, though the heart appears to have been damaged by rheumatic fever ten years before that.

The heart was greatly enlarged. There was evidence of developed mitral stenosis. The systolic blood-pressure was 125; and the electro-cardiogram (Pl. 12, Fig. 4) showed left branch block with auricular fibrillation and a tendency to bigeminal heart action.

She had previously been in hospital for three weeks in the spring of 1920, and had responded favourably to rest and treatment with digitalis. This time, however, she went steadily downhill, and died on January 3, 1922.

Case XV. A Jewish tailor, aged 54, had been off work for two years on account of shortness of breath. He had suffered from rheumatic fever twenty-five years previously; but, although the cardiac lesion probably dated from that time, he had enjoyed quite good health until the commencement of the present illness.

On admission to hospital, his heart was greatly enlarged. The full diastolic rumble of developed mitral stenosis was present. The electro-cardiogram (Pl. 13, Fig. 8) showed auricular fibrillation with right branch block, and in addition frequent ventricular complexes resembling more closely the normal type. The latter disappeared after a few days' rest. The blood-pressure was 130/80. His condition underwent considerable improvement during the month that he was in hospital, but soon relapsed after his return home, and he died four months later.

Case XVI. A Japanner, aged 55, was admitted to hospital as an urgency on May 10, 1922, having been suddenly seized with acute pain in the chest, and with intense dyspnoea, while he was on his way to business that morning. He had had six or seven similar but less severe attacks during the previous two years. He played cricket till 1914, but had noticed slight symptoms even before that date, and had been much worse since an attack of pneumonia in 1918.

On admission he was extremely dyspnoeic and cyanosed, and the heart-rate was 140. There was moderate cardiac enlargement, with all the signs of aortic stenosis and slight incompetence. His blood-pressure was 105/65.

His condition rapidly improved, the heart-rate falling to 64, and he was discharged on May 27. He was able to resume work at the end of July, and, apart from a minor attack in September 1922, he has had no recurrence of severe symptoms up to the present time.

Electro-cardiograms (Pl. 16, Fig. 13 a) taken in May, September, and October 1922 showed right branch block. No subsequent records were taken till July 1925, when the ventricular deflexions (Pl. 16, Fig. 13 b) were found to resemble much more closely the normal complex.

Case XVII. An ex-service postman, 25 years of age, came up for a final award before the Ministry of Pensions in September 1922. He had been buried by a shell-burst in 1917, and was subsequently invalided out of the army with 'neurasthenia'.

From his documents it appeared that while in hospital at Boulogne electro-cardiographic examination had revealed some abnormality, but what that abnormality was we have been unable to ascertain. However, a record taken on

October 3, 1922, showed right branch block. His principal symptoms were nervousness and attacks of dizziness. The heart was not enlarged. The second sound was clear, but a long systolic murmur was audible at the apex. From October 1922 up to the present date he has experienced no difficulty in performing his duties as an outdoor postman. His clinical condition has distinctly improved, though the electro-cardiogram remains unchanged.

Case XVIII. A clerk, aged 23, had been easily tired, short of breath, and subject to palpitation on exertion since the age of 18, when he was confined to bed for ten weeks with 'subacute rheumatism'. He caught cold in November 1921, and his symptoms became aggravated.

When examined a month later he was found to be very poorly developed but moderately nourished, and the organs other than the heart seemed normal. The left heart was much enlarged. The first sound was short and pure. The second sounds were sometimes double, and were accentuated in the pulmonary area. The signs suggested an organic congenital condition. A month later, while apparently steadily improving, he developed fever and a short dry cough, and died without any further local manifestations.

Case XIX. A pavement artist and old soldier, aged 60, since discharge from the army in 1917 had been subject to dyspnoea and sudden attacks of pain in the chest, which spread down the left arm as far as the fingers. He stated, however, that he had had occasional attacks of pain for some years previously.

The superficial arteries were markedly thickened. The heart was moderately enlarged, the sounds were faint, and the first sound was definitely reduplicated. There was a to-and-fro aortic murmur. The blood-pressure was 140/90. There was no evidence of congestion. The Wassermann reaction was negative. He was discharged from hospital considerably improved, but was not able to resume work, and died at home seven months later; the cause of death being stated as 'Bright's disease'.

Case XX. A cooper, 64 years of age, who had been in bed with a cold for three days, while in a tram-car returning to his work suddenly developed a right hemiplegia with aphasia. He had had small-pox and rheumatic fever many years previously. His cerebration was very slow. The heart was moderately enlarged. The sounds were feeble and impure. The blood-pressure was 140/100. The electro-cardiogram showed auricular fibrillation with right branch block. The hemiplegia rapidly cleared up, and he is working at the present time, though an electro-cardiogram taken fifteen months after his discharge from hospital showed no change in the ventricular complex.

Case XXI. A professional man, aged 62, complained of shortness of breath and occasional swelling of the feet.

The heart did not appear to be enlarged. The sounds were weak, but there was no evidence of any valvular lesion. The electro-cardiogram showed right bundle branch block with occasional extra-systoles. The blood-pressure was 140/85.

He has now been under observation for over a year, and there is no indication that the lesion is progressive.

Case XXII. A married woman, aged 34, was admitted to hospital in October 1924, complaining of epistaxis, headache, and vomiting. Her illness dated from a miscarriage in May 1922. Apart from high blood-pressure there was no evidence of cardiovascular disease. The urine contained blood and albumin. The urea concentration test gave only 0.8 per cent., and the blood urea was 260 mg. per 100 c.c.

A week after admission there was another attack of profuse haemorrhage, from which the patient did not recover.

A chance electro-cardiogram revealed right branch block.

? Rhe
? Enge ✓

Alt A1 ✓

3 Myoc ✓

Myoc ✓

BPT ✓

Case XXIII. A rather stout, extremely nervous and introspective married woman, aged 66, had complained of pain in the chest for the past fifteen years, and had been an invalid for many years previously. She had been able to take life very easily, and was accustomed to go abroad in the winter to escape the bad weather. The pain began in the neighbourhood of the angle of the right scapula and spread down both arms on the outer sides as far as the elbows, and down the inner sides as far as the tips of the ring and little fingers. Sometimes it came through to the front of the chest at the level of the second and third ribs. Frequently it came on at night in bed, or when lying down during the day, when it could be relieved by standing up. The heart did not appear to be enlarged. There was a soft apical systolic murmur. The systolic blood-pressure was 145.

The markedly neurasthenic temperament of the patient, together with the absence of any definite physical signs suggestive of organic heart disease, made one inclined rather to discount the history of the subjective symptoms. In addition she had suffered for some years from a 'dropped' right kidney, and much of her discomfort was undoubtedly attributable to this condition.

Electro-cardiographic examination, however, showed right branch block, and the patient died suddenly, and without warning, a month later.

Case XXIV. A retired school teacher, 61 years of age, who gave a rather indefinite history of subacute rheumatism, had known that his heart was affected since an attack of influenza sixteen years previously; but he had suffered little inconvenience from it until he developed heart failure in the winter of 1920. This appeared to be due to the onset of auricular fibrillation. He was in hospital for six weeks at that time. He improved greatly with rest and treatment, but his symptoms returned two years later, and gradually increased in severity. He was readmitted to hospital on January 31, 1925, with intense dyspnoea, oedema of the legs, and other evidence of advanced heart failure. His heart was greatly enlarged, and the full diastolic rumble of developed mitral stenosis was present. An electro-cardiogram (Pl. 14, Fig. 9) taken on February 12 showed auricular fibrillation with a ventricular rate of 160, and right branch block. On February 13 he had an epileptiform attack, and on the 14th a series of similar attacks from which he did not recover.

IV. Summary.

1. Twenty-four cases, all of which gave a typical electro-cardiogram of bundle branch block, have been studied, and their after-histories followed up.

2. Fourteen of these patients have died: ten within one year, and three others within eighteen months of coming under observation. Seven patients died of progressive heart failure with venous congestion, two of acute 'heart attacks', and five from causes not directly connected with the heart.

3. The remaining ten patients are alive at the present time. One has now been under observation for more than four years, and two for more than three years. Of these, seven are enjoying quite good health, and are able to carry on a fairly active life. But in one only of our cases has there been any evidence that the lesion is tending to clear up.

4. Twenty of our patients were men and four were women. Twenty were between 40 and 70 years of age.

5. The onset appears generally to be insidious, but may occasionally be abrupt. The principal symptom in most of our patients was either shortness of

THE CLINICAL ASPECT OF BUNDLE BRANCH BLOCK 111

breath (13 cases) or pain of an anginal nature (8 cases). Cardiac enlargement was well marked in 14 cases. The superficial arteries were obviously diseased in five cases. There was definite hypertension in 11 cases, and an associated valvular lesion in 11 cases. Auricular fibrillation was present in 5 cases, and complete a.-v. block in one case.

6. The condition appears generally to be due to a secondary fibrosis of the heart muscle. If the lesion be localized the prognosis is favourable, but if it be part of a widespread degenerative process the outlook is grave.

The striking immunity of the left branch, which was involved in only one case in our series, is probably to be explained by its anatomical disposition and by its richer blood-supply.

7. The frequency of the condition has probably been under-estimated, owing to the fact that it can only be recognized by electro-cardiographic methods. Its presence indicates a definite myocardial lesion, but if unaccompanied by signs of cardiac insufficiency is not necessarily of grave prognostic significance.

We are indebted to the physicians of the Manchester Royal Infirmary for the facilities afforded to one of us (J. C. B.) for studying cases under their care in the hospital.

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BPT
6½

Myoc
9

Phen
4½

Cong
1

Σ
1

Nel
2

24



Fig 4 (Case 14)

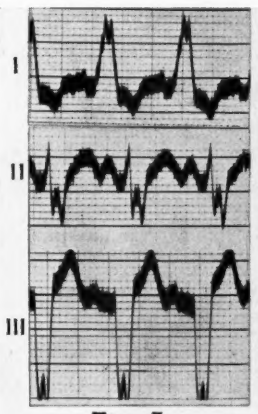


Fig 5
(Case 1)

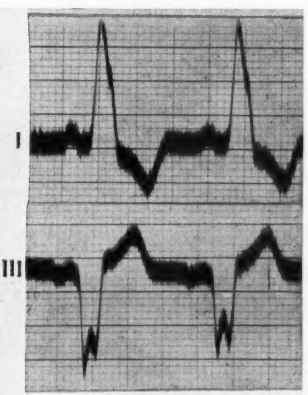


Fig 6
(Case 11)



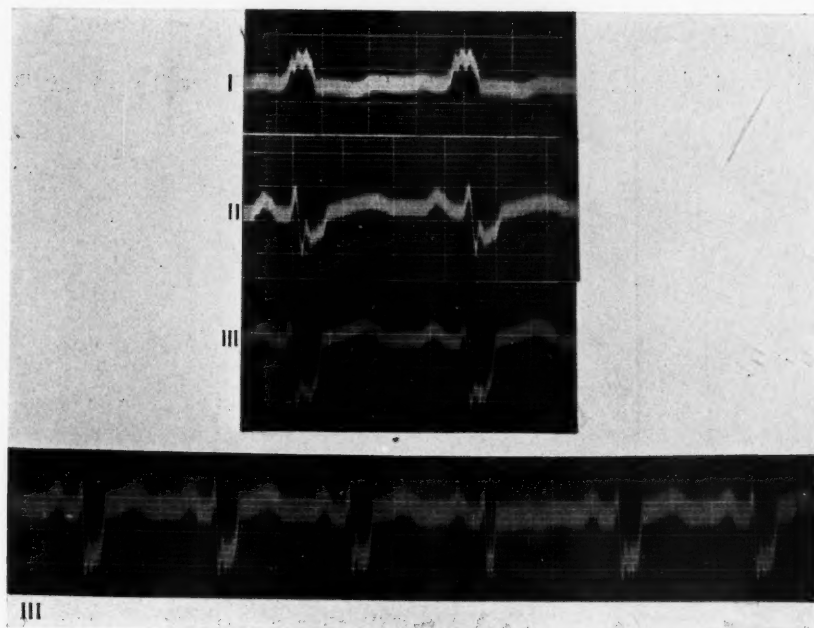


FIG. 7 (Case 13)

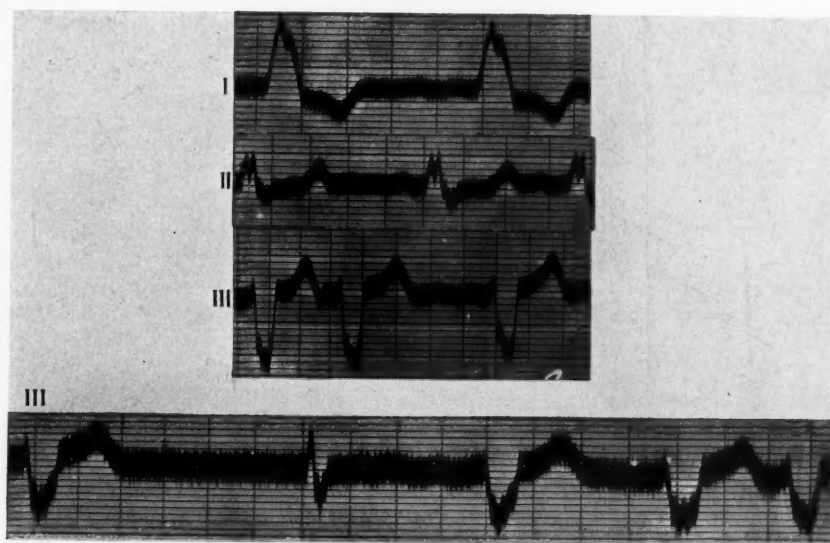


FIG. 8 (Case 15)



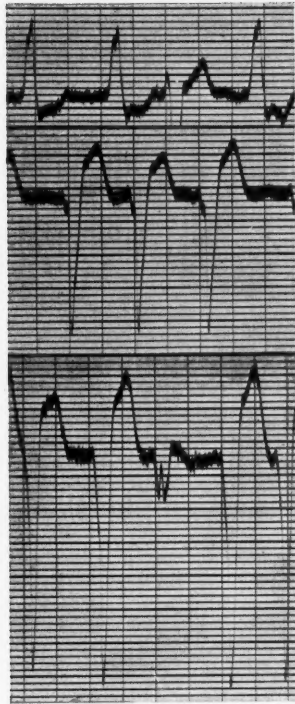


FIG. 9 (Case 24)

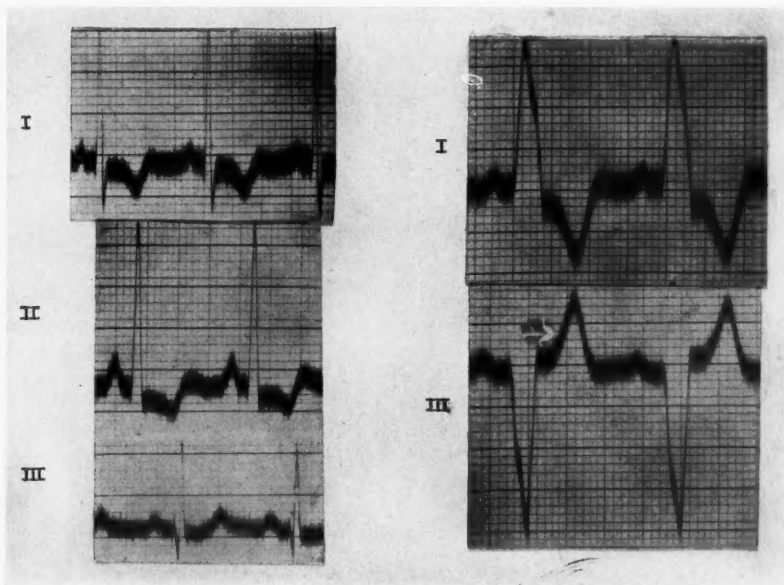


FIG. 14 (Case 5). *a*, 11 Jan. 1922; *b*, 21 Dec. 1922

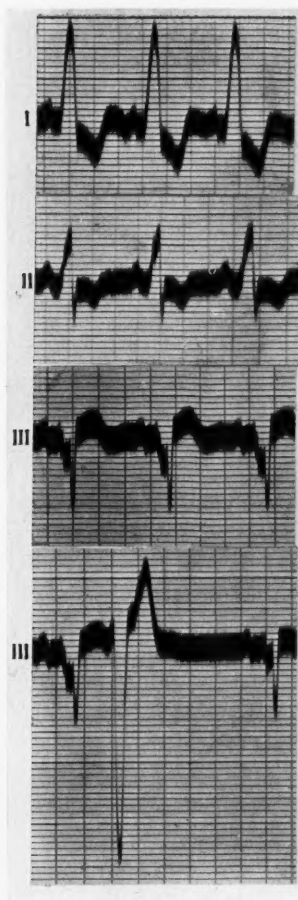


FIG. 10 (Case 12)

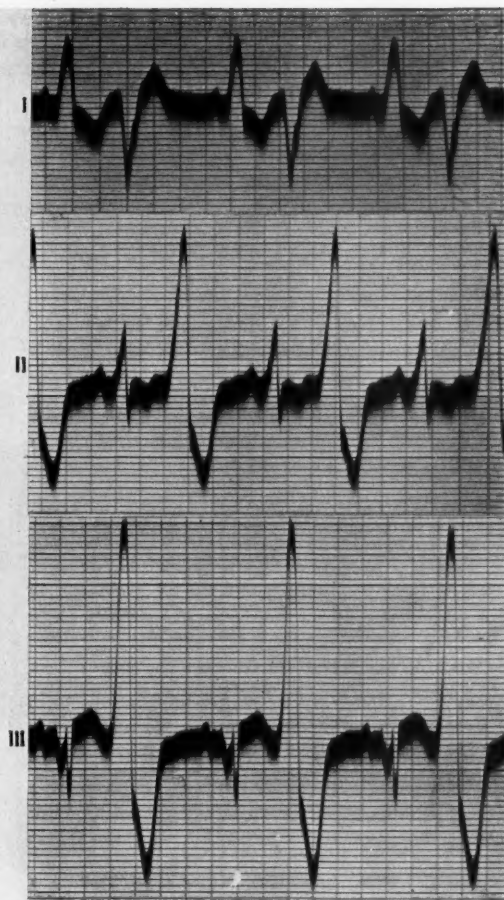
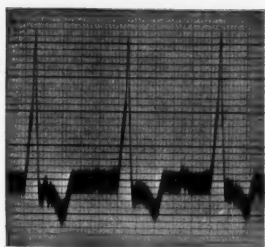
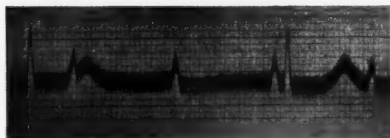


FIG. 11

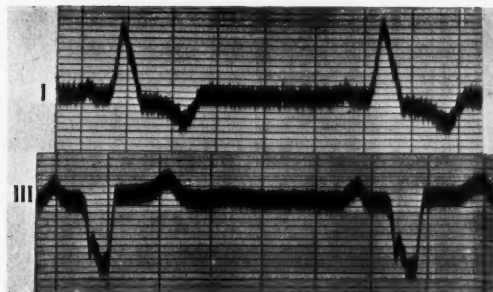


a

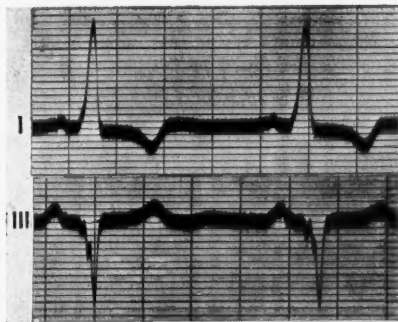


b

FIG. 12 (Case 3)
a, 4 July 1919; *b*, 18 Oct. 1919



a



b

FIG. 13 (Case 16)
a, 16 May 1922; *b*, 10 July 1925



HEART FAILURE WITH NORMAL RHYTHM¹

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IN 1922 Mackenzie (18), writing of auricular fibrillation, asserted that '60 or 70 per cent. of all cases of serious heart failure met with in practice owe the failure directly to this condition, or have the failure aggravated by its presence'. The truth of this statement is now generally recognized. In the great majority of patients with severe cardiac failure and oedema the auricles are fibrillating and the ventricular action is irregular. The extended use of cardiographic methods in recent years has still further focused attention on the disorders of cardiac rhythm and their association with failure. The result has been that heart failure with persistence of normal rhythm has been rather ignored, and that the significance, if any, of the absence of auricular fibrillation is doubtful.

While there are published series of cases of failure with auricular fibrillation and of failure with non-valvular disease ('chronic myocarditis') without relation to the cardiac rhythm, we can find no collected series of cases of heart failure with persistence of normal rhythm such as is here described. Yet one must suppose that the rhythm in failure is not fortuitous, but has some meaning. We have therefore tried to determine the significance of the cardiac rhythm ruling in failure by the investigation of cases failing with normal rhythm.

Method. One hundred cases of severe heart failure with normal rhythm have been investigated clinically, and 48 of them also by necropsy. As it is generally accepted that in the acute infections, infective endocarditis (16) and the rheumatic carditis of children (21), the heart commonly fails with normal rhythm, such cases have been excluded. Patients below the age of 20 years and over the age of 70 have also been excluded. With these exceptions there has been no selection.

Any artificial classification of a disorder of function into clinical or pathological groups is open to criticism, and particularly is this true of heart failure, where many different factors may be operating together to produce it. But for the purposes of presentation and discussion some grouping of our cases is necessary. We have adopted the following clinical classification as being the most convenient for our purpose:

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² Working under the Paterson Bequest.

³ Assisted by a grant from the Medical Research Council.

Group I. Cardiovascular syphilis includes all our cases in which this condition was found.

Group II. High blood-pressure includes all those with raised blood-pressure uncomplicated by cardiovascular syphilis or rheumatic heart disease.

Group III. Chronic pulmonary includes all those with advanced chronic lung disease uncomplicated by cardiovascular syphilis, high blood-pressure, or rheumatic heart disease.

Group IV. 'Primary myocardial' includes all those in which no 'cause' of failure was clinically apparent.

Group V. Rheumatic includes all those with rheumatic heart disease, whether or not other 'causes' of failure were also present.

Group VI. Unclassified includes those in which the necropsy findings did not justify their inclusion in any of the previous groups, and those without necropsy and with insufficient clinical evidence on which to base a diagnosis.

This classification, though clinically convenient, is admittedly hybrid. Thus it rests mainly on the pathological basis of the failure, e.g. cardiovascular syphilis, chronic lung disease, &c., but partially on the inferred mechanism of the failure, e.g. high blood-pressure. Also, by employing such a rigid method, a case has at times been included in a group in which the chief cause of the failure was one other than the lesion which led to its inclusion in that particular group. Nevertheless it has the advantage of being based on clinical or pathological fact and not on clinical judgement as to the predominating factor at work.

In the discussion to follow we have attempted to differentiate clearly between the anatomical (pathological) basis of the failure and the inferred physiological mechanism of its production. A patient does not die of the morbid changes found at necropsy, but of the disorder of function resulting from a pathological process which leads directly or indirectly to the anatomical changes. But it is from the morbid changes found at necropsy that the pathological process at work, and sometimes the mechanism of the failure, can be deduced. We have been particularly interested in the cardiac rhythm associated with the different physiological types of failure. Under each of the above groups, therefore, the pathological basis of the failure in our cases will first be described. The current and generally accepted interpretation of the mechanism or actual cause of the failure will then be indicated and briefly discussed. Our evidence will then be brought forward to show the nature of cardiac rhythm usually associated with the particular form of failure. Finally a comparison of these findings will be made in an attempt to determine the causes and circumstances which decide whether auricular fibrillation shall supervene or normal rhythm persist in severe heart failure.

It is severe heart failure that has been studied, because our object has been to deal with that type of case in which one would expect to find auricular fibrillation if it were going to occur at all. By severe heart failure is meant that the patient was of necessity confined to bed with breathlessness and oedema of the legs. Cardiac pain has not been considered as a factor in deciding the degree

of failure present. In every case, therefore, the heart failure was of the 'congestive' type. The term 'heart failure' is retained to indicate the symptom-complex usually associated with that condition, and it does not imply that the heart is primarily at fault. By normal rhythm we mean that the auricles are responding to the impulses arising naturally in the sino-auricular node. This definition includes auriculo-ventricular block, and sinus rhythm with occasional extra-systoles, but excludes auricular flutter and fibrillation, and paroxysmal tachycardia.

It soon became apparent that severe heart failure with normal rhythm is relatively uncommon, and so it became necessary to search at a number of Poor Law hospitals over a long period. When each patient was first seen, a detailed history was taken and direct inquiry made for acute rheumatism, chorea, syphilis, and chronic bronchitis. A history of rheumatism was not accepted unless the illness occurred in early life and showed features characteristic of this disease; rheumatic pains in adult life alone have not been regarded as sufficient evidence. Normal rhythm was demonstrated by polygram in all cases, and confirmed by electro-cardiogram where possible. The size of the heart was judged by the position of the apex-beat and often by radioscopy. The blood-pressure was recorded by the auscultatory method in the brachial artery. The first reappearance of the systolic sound when the cuff pressure was reduced has been taken as the systolic pressure, and the sudden diminution in intensity of this sound when the cuff pressure was further reduced has been taken as the diastolic pressure. The fundi were always examined. The Wassermann reaction of the blood was performed in all, usually by two independent laboratories. The blood-urea was estimated by the urease method and is expressed in milligrams of urea per 100 c.c. of blood. The urea-concentration test was performed, in certain cases, as described by MacLean (20).

All patients, whenever possible, have been kept under observation until they died. The large majority were seen for the last time within a few days of death and the rhythm remained normal. Seven developed auricular fibrillation subsequent to our first examination; but even here it will be noted that cardiac failure began and progressed in the presence of normal rhythm.

Group I. Cardiovascular Syphilis.

Twenty-one cases are included in this group. Of these, ten showed syphilitic aortitis at necropsy. In nine others without necropsy the Wassermann reaction was positive, aortic incompetence or aortic aneurysm was present, and no history of rheumatism was obtained. The diagnosis of cardiovascular syphilis in the remaining two cases requires special consideration. Case 15 had heart failure without aortic incompetence, but the Wassermann reaction was positive. He improved greatly after salvarsan, mercury, and iodide, and died four years later (no necropsy). Case 24, who was treated for syphilis at the age of 20, had severe failure with aortic stenosis and incompetence, complete heart-block, and

a left bundle-branch lesion. Yet the Wassermann reaction was negative when performed by two independent laboratories. Mercury and iodide was then begun, and now, two years later, he is still at work.

Cases without clinical evidence of cardiovascular syphilis, with negative Wassermann reactions, although giving histories of primary syphilitic infection, have not been included in this group. Nor even with positive Wassermann reactions have such cases been accepted if another adequate cause of failure was apparent.

1. *Clinical features.* The histories and clinical features of the cases in this group are summarized in Table I.

The average age was 55; eighteen were males and three females. Four gave a definite history of primary syphilis, and two of venereal infection of doubtful nature. Eight had suffered from pain in the chest, possibly cardiac in origin; but in only one (99) was a typical history of sternal or anginal pain obtained. Seventeen cases had aortic incompetence with or without clinical evidence of aneurysm. In two of them (13, 55) aortic diastolic murmurs were heard during life, but necropsy showed the aortic cusps to be intact. Two cases had in addition aortic stenosis as evidenced by a systolic thrill and, in one, by necropsy. Two had aortic aneurysm without aortic incompetence. Two showed complete heart-block, and one prolongation of the P-R interval without dropped beats. Evidence of a bundle-branch lesion was found in two of the patients examined with the electro-cardiograph. Orthopnoea, oedema of the bases of the lungs, oedema of the feet and legs, were constant features, often accompanied with ascites. The liver was invariably enlarged, frequently to below the umbilicus. The urine usually contained albumin and occasionally a few granular or hyaline casts. The degree of cyanosis and venous congestion was variable, and the clinical picture of these cases did not differ materially from that of cases of mitral disease failing with auricular fibrillation. All with one exception died with progressive cardiac failure and increasing oedema and ascites. Case 13 died suddenly from partial rupture of an aneurysm of the aortic arch. The pulse was seldom frequent and the average rate was only 92. Extra-systoles were never numerous and were only recorded in five patients; pulsus alternans was only observed in four. The arteries were unduly thickened in four cases only, and the blood-pressure was pathologically raised in three of these (24, 45, 69), and in one other (13). Cheyne-Stokes respiration was frequently seen, often to an extreme degree. Cases 4 and 54 presented the clinical picture of chronic bronchitis and emphysema with secondary heart failure. Clinically there were no signs of aneurysm or aortic incompetence; and as radioscopy could not be performed, positive Wassermann reactions alone led to tentative diagnoses of cardiovascular syphilis, which were confirmed by necropsy.

All, with the two following exceptions, maintained normal rhythm during the whole period of observation, which often extended to the day of death. Case 5 had one short attack of paroxysmal auricular fibrillation while under observation, and at a time when he was not under the influence of digitalis. This patient

alone out of the twenty-one gave a history of rheumatic fever in childhood. Case 45 developed auricular fibrillation after taking tinct. digitalis (B. P.) one drachm daily for 72 days. Seven days later right hemiplegia with aphasia, probably of embolic origin, suddenly appeared. Though digitalis was discontinued the arrhythmia persisted until death ten weeks later. There was no history of rheumatism, but as digitalis in large doses is capable of inducing auricular fibrillation, this may have been the cause (ref. 23).

Eighteen cases have died. In these the average duration of life from the onset of dyspnoea was several years, but from the onset of oedema it was ten months. Three are still alive; of these, two (20, 24) continue in fair health three years after the onset of oedema, and the third (22) remains in hospital two years after its onset. Of the two who alone received antisyphilitic treatment for the cardiac condition, one (24) is alive and at work two years later, and the other (15) died four years after the onset of oedema. The others were not treated for syphilis either because failure was too advanced or for other reasons.

Once oedema develops the prognosis in cardiovascular syphilis is bad, but even then beneficial results may be obtained by antisyphilitic treatment. The ordinary clinical manifestations of cardiovascular syphilis may be absent. If radioscropy cannot be performed, an aneurysm without aortic incompetence can easily be missed, particularly if there is chronic lung disease to which the failure might be attributed. The Wassermann reaction should be performed not only in all cases of aortic incompetence in adults, but also in unexplained heart failure with normal rhythm. It must be remembered that the Wassermann reaction may be negative even in untreated syphilitic aortitis proved *post mortem* (refs. 3, 17, 22, 25). Case 10 of this series is a typical instance; while Case 4, which showed syphilitic aortitis at necropsy, gave a positive reaction when examined in one laboratory and simultaneously a negative when examined in another. Therefore a negative reaction should not preclude a careful inquiry for a history of syphilis. Even if the Wassermann reaction is negative, especially if a history of a primary sore is obtained, energetic antisyphilitic treatment should be given to patients with failure showing the cardiac lesions common in syphilis.

2. *The cause of failure.* Seventeen of our twenty-one cases had aortic incompetence. Of the ten cases on which post-mortem examinations were performed, seven showed occlusion or stenosis of one or both coronary arteries, the right being more frequently affected. In some there was found consequent focal fibrosis of the myocardium.

Chronic bronchitis and emphysema contributed to the failure in Cases 4 and 54. High blood-pressure was the chief cause of failure in Case 45, and may have been an additional factor in Cases 13, 24, and 69.

Thus the actual cause of heart failure in this group, except in Case 45, was interference with the blood-supply of the cardiac muscle and its inability to cope with the valvular disability, not generalized syphilitic disease of the myocardium.

3. *The rhythm.* Cardiovascular syphilis was associated with 21, and was the cause of failure in 20 of our 100 cases of heart failure with normal rhythm.

The large majority are known to have died with normal rhythm persisting. In two only did auricular fibrillation occur during the subsequent course of failure. In one it might be explained by the history of acute rheumatism in childhood and in the other by prolonged administration of digitalis.

As a contrast to this series, we have summarized, in Table II, 60 unselected cases of auricular fibrillation, with or without cardiac failure. The first 45 of these cases have already been published (4). The Wassermann reaction was performed as a routine, and was positive in the following five only: No. 3, mitral stenosis, aortic incompetence, history of rheumatism. At necropsy the diagnosis of these valvular lesions was confirmed, but the aortic lesion was found to be of rheumatic origin and there was no syphilitic aortitis. No. 19, mitral stenosis; no clinical evidence of cardiovascular syphilis. No. 36, no history of rheumatism, no valvular lesion. Necropsy showed syphilitic aortitis with myocardial fibrosis. No. 45, no history of rheumatism, syphilitic hemiplegia, exophthalmic goitre. No. 58, no history of rheumatism, aortic aneurysm (radioscopy).

Cardiovascular syphilis therefore appears to be often a cause of advanced heart failure with normal rhythm, but rarely of failure with auricular fibrillation. Moreover, in cases with auricular fibrillation, even with positive Wassermann reactions, the disorder of rhythm can sometimes be attributed to a chronic rheumatic infection of the heart-muscle, to exophthalmic goitre, maybe to the excessive administration of digitalis, without postulating syphilis as a cause of the arrhythmia.

This conclusion, that syphilis is seldom a cause of auricular fibrillation, is in accordance with the literature. In 126 cases of permanent auricular fibrillation Romberg (24) found 13 (approximately 10 per cent.) syphilitic. From a study of 128 cases of auricular fibrillation, Levine (14) concluded that syphilis is not an important factor in its production. It was present in eleven, i. e. 8.6 per cent., while the Wassermann reaction was positive in 12 per cent. of all cases admitted to the wards. Among 28 cases, 9 of his own and 19 reported, in which auricular fibrillation was certainly present during life, and a special pathological examination was made after death, Flöystrup (8) found that only two (i. e. 7 per cent.) were syphilitic.

Explanation of Tables.

Rh. = rheumatism.	A. S. = aortic stenosis.
S. = syphilis.	M. S. = mitral stenosis.
V. D. = venereal disease.	C. H. B. = complete heart-block.
Ex. G. = exophthalmic goitre.	P. H. B. = partial heart-block.
Ad. P. = adherent pericardium.	B. B. L. = bundle-branch lesion.
An. = aneurysm.	+ = slight.
Aort. = aortitis (p.m.).	+ + = severe.
A. I. = aortic incompetence.	N. = normal.

Figures in last column indicate the number of days before death on which the patient was last seen and normal rhythm noted. F. indicates that fibrillation occurred.

TABLE I. Group I. Cardiovascular Syphilis.

Case.	Age.	Sex.	History.	W. R. Lab.	Dyspnoea (years).	Oedema (months).	Dead.	Necropsy.	Cardiac Lesions.	Pulse-rate.	Katira-astholes.	Pulsus alternans.	Blood-pressure.	Cheyne-Stokes Respiration.	Blood-urea.	Number of days before death last seen.
3	47	M	0	1	0	7	Yes	—	A.I., B.B.L.	112	0	+	120	0	0	28
4	63	M	0	+	3	15	Yes	Yes	An., A.I.	96	+	0	145	0	53	9
5	51	M	0	+	0	?	Yes	—	An., A.I.	80	0	0	140	0	0	?
9	38	M	0	+	4	24	Yes	—	A.I.	92	0	0	140	+	100	10
10	51	M	S.	neg.	0	16	Yes	Yes	A.I., A.S.	80	0	0	150	0	0	2
13	69	F	0	+	1½	12	Yes	Yes	An., A.I.	84	0	0	175	0	43	5
15	41	M	0	+	4	48	Yes	—	—	90	+	0	110	0	79	?
20	69	M	0	+	—	—	No	—	A.I.	90	+	+	120	0	30	—
22	48	F	0	+	—	—	No	—	A.I., C.H.B.	40	0	0	130	0	28	—
24	60	M	S.	neg.	—	—	No	—	A.I., C.H.B.	44	0	0	180	0	51	—
35	57	M	0	+	7	—	Yes	Yes	An., A.I.	84	0	0	190	+	60	—
40	52	M	S.	+	1	1	Yes	Yes	A.I.	95	0	0	145	+	48	1
45	57	M	S.	+	3	2	Yes	Yes	—	120	0	0	170	+	30	1
54	70	M	0	+	2½	5	Yes	Yes	An.	94	0	0	90	+	0	3
55	57	M	0	+	2	1	Yes	Yes	An.	104	+	+	135	+	110	1
56	65	M	0	+	4	1	Yes	Yes	A.I., A.I.	72	0	0	165	+	38	20
55	55	M	0	+	2	2	Yes	Yes	An.	90	0	0	130	+	0	3
64	48	M	0	+	4	6	Yes	—	A.I.	88	0	0	210	0	30	1
69	60	M	0	+	7	6	Yes	—	A.I.	82	0	0	180	+	0	5
78	64	F	0	+	1	1	Yes	—	A.I.	98	0	0	115	0	0	14
85	60	M	V.D.	+	4	19	Yes	—	A.I.	108	0	0	140	0	41	1
99	42	M	0	+	½	1	Yes	Yes	A.I.	108	0	0	140	0	0	1

4. *Necropsy Reports. Case 4. Syphilitic aortitis with severe atheroma and dilatation.* Slight syphilitic endocarditis of competent aortic valves. Moderate atheroma of coronary arteries, with moderate stenosis of orifice of right but no stenosis of orifice of left. Other valves normal. Great hypertrophy of left and slight hypertrophy of right ventricle. Slight, patchy, microscopic fibrosis of myocardium. Syphilitic *hepar lobatum*. Congestion of liver, spleen, and kidneys; calculus in left kidney. Microscopic examinations were made of the aortic valve, interventricular septum, liver, spleen, and left kidney.

Case 10. Syphilitic aortitis, with atheroma. Syphilitic endocarditis. Thickening, rigidity, and retraction of aortic cusps causing great aortic stenosis and incompetence. Moderate stenosis of both coronary orifices. Other valves normal. No visible abnormality in myocardium. Great hypertrophy of left ventricle. Congestion of liver and kidneys. Microscopic: aortic valves, ascending aorta and kidney.

Case 13. Syphilitic aortitis with calcareous atheroma, aneurysmal dilatation and complete rupture of aorta. Stenosis of trachea. Calcareous atheroma of competent aortic valves. Other valves normal. Stenosis of orifices of both coronary arteries. Small heart with no relative enlargement of any chamber. No macroscopic fibrosis of myocardium. Microscopic: ascending arch and transverse arch of aorta.

Case 35. Syphilitic aortitis with dilatation of ascending aorta. Syphilitic endocarditis of aortic valve causing thickening of cusps and incompetence. Other valves normal. Great hypertrophy and dilatation of left ventricle, slight of other chambers. Double pleural effusion. Microscopic: aortic valve and aorta.

Case 40. Syphilitic aortitis with aortic incompetence. Occlusion of orifice of right coronary artery. Bilateral pleural effusion.

Case 45. Cardiovascular hypertrophy. Syphilitic aortitis and considerable atheroma. Aortic and other cardiac valves normal. Slight atheroma, but no stenosis of coronary arteries. Great hypertrophy of left ventricle (heart 18 oz.). Small patch of fibrosis, probably syphilitic, in upper part of posterior wall of left ventricle; myocardium otherwise normal. Ante-mortem thrombi in both auricles. Congestion, fatty degeneration of ascending tubules of Henle, and slight chronic interstitial nephritis in kidneys (11 oz.); hypertrophy of renal arteries; fatty atheroma of arterioles. Confluent 'back-pressure' atrophy and regeneration in liver. Microscopic: ascending aorta, fibrous patch in myocardium, liver, and kidney.

Case 54. Syphilitic aortitis and severe calcareous atheroma with diffuse aneurysmal dilatation of ascending aorta and aortic arch. Slight thickening of cusps of competent aortic valves. Coronary orifices not stenosed. Great hypertrophy of left and considerable hypertrophy of right ventricle. Ball thrombus in right ventricle. Syphilitic fibrosis binding the right auricle and commencement of pulmonary artery to the aortic aneurysm, and implicating the endocardium and myocardium of the upper part of the anterior wall of the right ventricle and the upper third of the interventricular septum; patch of fibrosis in apex of left ventricle. Very slight chronic interstitial nephritis: a very few fibrotic glomeruli surrounded by small areas of fibrosis in cortex of kidney. Confluent 'back-pressure' atrophy and regeneration of liver. Microscopic: aorta, right and left ventricles, interventricular septum, kidney, and liver.

Case 55. Syphilitic aortitis. Aortic cusps normal but aortic ring dilated; aortic incompetence. Other valves normal. Right coronary orifice almost occluded; coronary arteries otherwise normal. Hypertrophy of all chambers, particularly of left ventricle.

Case 56. Syphilitic aortitis and severe atheroma. Diffuse dilatation of ascending aorta and aortic arch with sacculatation at junction of the two. Considerable thickening by syphilitic endocarditis of cusps of incompetent aortic valves. Other valves normal. Considerable stenosis of orifice of right, but no stenosis of orifice of left coronary artery. Calcareous atheroma of both coronary arteries. Great hypertrophy of left and considerable hypertrophy of right ventricle. No macroscopic fibrosis of myocardium. Fatty degeneration of second convoluted tubules in kidneys. Microscopic: left posterier aortic cusp, ascending aorta, and kidney.

Case 99. Syphilitic aortitis with moderate atheroma. Syphilitic endocarditis, causing thickening and retraction of cusps of incompetent aortic valve. Other valves normal. Slight stenosis of right and extreme stenosis of left coronary orifice. Focal ischaemic fibrosis of myocardium. Hypertrophy of all chambers; considerable dilatation of left ventricle. Confluent 'back-pressure' atrophy of liver. 'Back-pressure' kidneys. Microscopic: ascending aorta.

Group II. High Blood-pressure.

To what extent arterial blood-pressure must be raised before it should be considered pathological is a matter of opinion. We have included in this group all uncomplicated cases with systolic blood-pressures of 160 or over, and diastolic blood-pressures of 100 or over, when they first came under our observation with failure. Those complicated by cardiovascular syphilis have been included in Group I, and those by rheumatic endocarditis in Group V. Patients giving a history of syphilis with negative Wassermann reactions and no evidence of cardiovascular syphilis, and those giving a history of rheumatism but no evidence of rheumatic endocarditis, have been placed in this group because the evidence of syphilitic or rheumatic heart disease was doubtful.

1. *Clinical features.* Twenty-three of the hundred cases of the series are included in this group, and their histories and clinical features are summarized in Table III. Of these, nineteen are dead, and necropsies were performed on nine. The average age was 54. Four gave histories of acute rheumatism, two of syphilis, and two of some venereal infection. The Wassermann reaction was negative in all. In the nineteen who have died the average duration of cardiac symptoms was: shortness of breath three years, oedema twelve months. Four are still alive one to three years after the onset of oedema.

The average pulse-rate on first examination was 97. In the majority apical systolic murmurs of varying length and intensity were heard; but apart from the doubtful inferences that might be drawn from these, clinical evidence of valvular lesions was absent. Eighteen (78 per cent.) had pulsus alternans, and seventeen had extra-systoles. The radial and brachial arteries were unduly thickened in fourteen, rather more than half; but high grades of hardness and tortuosity were seldom found. The urine always contained albumin. The majority showed signs of chronic bronchitis. Cheyne-Stokes respiration was observed in nine. The average blood-pressure on first examination was 200 systolic, and 125 diastolic. The blood-urea only once exceeded 86. Except one who died suddenly (no necropsy), all failed and died with increasing oedema.

All, with the three following exceptions, maintained normal rhythm during the whole period of observation, which often extended to the day of death. *Case 36* developed auricular fibrillation two years after the onset of oedema and three months before death. He gave a history of acute rheumatism and had been taking digitalis for a long time when the change in rhythm occurred. *Case 89* after three months was found to have fibrillation and he died ten days later. There was no rheumatic history. *Case 98* developed auricular fibrillation on the second day of digitalis administration (tincture, α xv, 6-hourly); there was no rheumatic history.

The clinical picture did not differ materially from that of patients failing with auricular fibrillation; but cyanosis and venous congestion were not so extreme unless there was much bronchitis, when it was sometimes mistaken for failure due to chronic pulmonary disease until the blood-pressure had been taken. Somewhat characteristic was the combination of pulsus alternans and extra-systoles, which often resembled the pulse of auricular fibrillation so closely that a polygram was essential for diagnosis. This fact may explain some cases of high blood-pressure erroneously thought to be failing with fibrillation.

If headache and vomiting, polyuria and frequency, renal retinitis, coma, or convulsions be taken as clinical evidence of renal disease, a renal element was present in four cases only. *Case 29*. Headache, nocturnal frequency, renal retinitis. Urine, alb. 1/3rd. Blood-urea 57. No coma or convulsions. No necropsy. *Case 41*. Death in coma with convulsions. A month before death, urea-concentration test 1.86; P.S.P. excretion, first hour 25, second hour 14, third hour 6. Blood-urea, day before death, 86. Necropsy. *Case 44*. Advanced renal retinitis. Blood-urea 50; urea-concentration test 3.3. Death without uraemic symptoms. Necropsy. *Case 59*. Headache, frequency, renal retinitis. Blood-urea, 184. Urea-concentration test 1.35. P.S.P. excretion, a trace only. Semi-comatose before death. No necropsy.

2. *The cause of failure.* The relationship between cardiac failure, high blood-pressure, and renal disease is still largely undetermined. It will be remembered that only patients showing the full picture of cardiac failure are here considered.

Allbutt divided arteriosclerosis with raised blood-pressure into the hyperpietic and the renal. Of the latter, two types are often differentiated, which are based on the assumption that two different pathological processes are at work: (1) primary high blood-pressure with arterial degeneration (hyperpietic arteriosclerosis) and secondary renal disease (arteriosclerotic kidney); (2) primary renal disease with secondary arterial hypertension and arterial degeneration (arteriosclerosis of renal origin). On the other hand, this division is questioned by those who believe that a single pathogenic factor causes both renal and vascular lesions to varying degrees. Professor Turnbull, in whose laboratory the histological examinations and many of our necropsies were made, considers that (1) high blood-pressure may be secondary to primary destruction of the kidney, and that (2) persistently high blood-pressure, by causing degeneration

of the intima and thus partly occluding arteries, may induce secondary ischaemic destruction of the kidney. The histological differentiation of the pathological processes in the two types of kidney is difficult; and the difficulty is increased by both kinds of process naturally tending to occur simultaneously in the later stages of the first type of kidney. Not only do ischaemic changes tend to complicate a primary nephritis which has led to persistently high blood-pressure, but a non-ischaemic nephritis may occur during the course of a hyperpiesis. When, therefore, both types of change occur in the same kidney, it may not be possible to judge by histological criteria alone whether the nephritis or the high blood-pressure occurred first. His opinion on the type of the kidneys in this group is based upon histological criteria arrived at tentatively by Miss Russell, who is at present working at the differentiation in his laboratory. By cardiovascular hypertrophy he means the hypertrophy of the heart, chiefly of the left ventricle, and the proportionate hypertrophy of the media of the muscular arteries, which together form the anatomical indication of clinical high blood-pressure (ref. 28).

Of our four cases which showed clinical evidence of renal disease, necropsy was performed in two. In Case 41 the essential changes in the kidney could not be attributed to ischaemia, and were sufficient to account for the cardiovascular hypertrophy. In Case 44 the changes were ischaemic in character and were doubtless secondary to the cardiovascular hypertrophy. Of the remainder who showed no clinical evidence of renal disease, necropsies were obtained in six. In 50, 57, and 88 the changes were essentially ischaemic, but in 57 they were complicated by a recent acute and subacute parenchymatous nephritis. In 26 no abnormality except congestion was observed in the kidneys with the naked eye, and microscopic sections were not made. In 46 and 89 the changes were apparently not ischaemic.

It appears that in the cases dealt with in this group a minority had primary renal disease, while the majority showed no more than ischaemic changes in the kidney, attributable to high blood-pressure.

The clinical lesion common to all was cardiac enlargement and high blood-pressure. The symptoms and signs were those of heart failure, and indications of renal disease were uncommon. It is unimportant for our argument to discuss how the increase in blood-pressure is brought about, though we have the impression, after comparing the clinical and post-mortem findings, that in the majority it is not the direct result of primary renal disease. These facts suggest that the failure is bound up with the high blood-pressure. Allbutt's conception of cardiac failure in hyperpiesia is that the peripheral resistance increases, and therefore a higher blood-pressure must be maintained to ensure adequate circulation of the blood. The heart therefore hypertrophies. If the increasing resistance imposes an insuperable load on the heart, failure supervenes as a confession of 'cardiac defeat'. Thus the histological changes in these hypertrophied hearts are very slight, which suggests that the failure is not due to the effects of primary organic disease, but to functional inefficiency of the hypertrophied myocardium to cope

with the increased peripheral resistance. The unknown cause of high blood-pressure may exert some deleterious effect upon the myocardium; and high blood-pressure does sometimes lead to coronary atheroma which, if advanced or complicated by thrombosis, will interfere with the blood-supply to the heart. Thus in two of our cases (26, 88) there was severe coronary disease which may have accelerated failure. In five others there was merely slight microscopic fibrosis, and in one parenchymatous degeneration.

The small proportion of primary renal cases in our series suggests that the majority die of uraemia or some complication. On the other hand, many hyperpiesics die of cerebral haemorrhage, and a fair proportion of progressive cardiac failure. There is little justification for applying the term cardio-renal to this latter group, i.e. hyperpiesia with failure; for they are neither primarily cardiac nor primarily renal, and the cardiac failure which obtrudes is merely secondary to the raised tension, whatever its origin. Hypertensive heart *failure* rather than hypertensive heart disease better describes the whole group.

3. *The rhythm.* There are few references in the literature to the incidence of auricular fibrillation in patients with high blood-pressure. Janeway (12) says that he has been 'somewhat impressed with the less frequent occurrence of fibrillation of the auricles in the insufficient heart secondary to high blood-pressure, as contrasted with valvular disease'. Allbutt (1) supposed that if auricular fibrillation does supervene in hyperpiesis the heart is primarily at fault or has become invaded by the arteriosclerotic process. The most definite statements are those made by Gallavardin (9), who says, 'La règle chez les hypertendus est que le rythme cardiaque conserve sa régularité jusqu'à la fin'; and in a more recent publication (10): 'Les grands Brightiques au cœur de bœuf avec énorme hypertension conservent d'ordinaire un pouls régulier jusqu'à la fin.' Yet in the same paper he states that auricular fibrillation is frequently associated with *moderate* hypertension (160-180 mm. of Hg), and expresses the view that this means not that cases of hypertension do not develop auricular fibrillation, but that the blood-pressure falls when the disorder of rhythm supervenes. To provide evidence on this point we have summarized, in Table II, sixty unselected cases of auricular fibrillation, in which, with rest and digitalis, dyspnoea and oedema disappeared. In the majority of these, normal rhythm was restored with quinidine. The systolic blood-pressure during auricular fibrillation, at a time when the ventricular rate was controlled with digitalis, is compared with that after the restoration of normal rhythm, when time had been allowed for the toxic effect of quinidine to wear off. Mackenzie (19) pointed out that in auricular fibrillation the arterial pressure is constantly varying, and that the mean tension cannot be determined by ordinary methods. The readings of systolic blood-pressure during auricular fibrillation were here obtained by slowly reducing the cuff pressure over the brachial artery and recording the point at which a systolic sound was first heard at the bend of the elbow. No attempt is made to justify this method theoretically, but it is believed that the figure so obtained does represent approximately the maximum systolic blood-pressure. When the ventricle is beating rapidly and

TABLE II. *The Blood-pressure and the Incidence of Syphilis in 60 consecutive Cases of Auricular Fibrillation, of which 43 were restored to Normal Rhythm with Quinidine.*

No.	Age.	Rheumatic History.	Diagnosis.	W. R. Blood.	Syst. B. P. (approx.) in Aur. Fib.	B. P. in Normal Rhythm.	
						S.	D.
1	58	+	M. S.	neg.	—	155	75
2	32	0	M. S.	neg.	—	120	90
3	36	+	M. S., A. I.	pos.	—	140	65
4	40	+	M. S.	neg.	—	125	85
5	35	0	M. S.	neg.	130	—	—
6	37	+	0	neg.	—	140	80
7	42	+	0	neg.	155	—	—
8	62	0	M. S.	neg.	—	125	70
9	49	0	0	neg.	155	160	90
10	30	+	M. S., A. I.	neg.	130	140	70
11	26	+	M. S.	neg.	105	120	65
12	26	+	M. S., A. I.	neg.	120	105	75
13	59	0	A. I., Ex. G.	neg.	110	105	45
14	23	+	M. S.	neg.	105	—	—
15	47	+	M. S.	neg.	125	115	80
16	51	0	0	neg.	180	—	—
17	30	+	M. S.	neg.	125	120	65
18	49	0	Ex. G.	neg.	110	120	60
19	42	0	M. S.	pos.	115	140	85
20	48	0	M. S.	neg.	135	130	85
21	58	0	M. S.	neg.	130	130	75
22	47	0	M. S.	neg.	130	145	70
23	63	0	0	neg.	115	110	70
24	45	+	M. S.	neg.	125	140	80
25	44	0	M. S.	neg.	130	110	56
26	52	+	M. S.	neg.	190	170	90
27	48	0	M. S.	neg.	165	—	—
28	44	+	M. S.	neg.	150	—	—
29	56	+	M. S.	neg.	225	230	100
30	32	+	0	neg.	135	130	80
31	65	0	0	neg.	125	130	70
32	50	+	0	neg.	150	165	80
33	35	+	M. S.	neg.	105	90	60
34	22	+	M. S.	neg.	145	—	—
35	38	0	M. S.	neg.	130	140	85
36	37	0	Aort.	pos.	130	115	65
37	34	0	M. S.	neg.	115	110	70
38	32	+	M. S.	neg.	110	125	70
39	43	0	Ex. G.	neg.	135	130	65
40	45	+	M. S.	neg.	125	125	70
41	52	0	0	neg.	190	—	—
42	30	0	M. S.	neg.	135	110	65
43	44	0	0	neg.	130	115	80
44	30	0	M. S.	neg.	120	—	—
45	43	0	Ex. G.	pos.	120	130	75
46	39	0	M. S., Ex. G.	neg.	125	130	55
47	15	+	M. S.	neg.	—	—	—
48	43	+	M. S., Ex. G.	neg.	105	115	60
49	45	0	Ex. G.	0	160	—	—
50	37	+	M. S., A. I.	0	—	—	—
51	64	0	0	neg.	170	165	90
52	63	0	0	neg.	145	130	80
53	50	0	Ex. G.	neg.	175	—	—
54	42	+	M. S.	neg.	120	125	75
55	14	+	Ad. P.	neg.	—	—	—
56	30	+	M. S.	neg.	120	—	—
57	51	0	M. S.	neg.	180	—	—
58	59	0	An.	pos.	160	—	—
59	38	+	M. S.	neg.	—	115	75
60	26	0	0	0	—	160	80

irregularly such readings are variable; but when beating slowly and more evenly under digitalis control, they are fairly constant. An examination of Table II shows that the maximum systolic blood-pressure so measured during auricular fibrillation never differed by more than 25 mm. Hg from the systolic blood-pressure in the same case after normal rhythm had been restored. Gallavardin's statement that the blood-pressure falls with the onset of auricular fibrillation to rise again with the restoration of normal rhythm is only true when there are coincident changes in ventricular rate (cf. Lewis (15)). If the comparison is made, not immediately the change in rhythm occurs, but when the ventricular rates are approximately the same, and the clinical state of the patient is comparable, the blood-pressure of an individual during fibrillation does not differ much from his blood-pressure during normal rhythm.

Auricular fibrillation has been divided into rheumatic (younger, and with mitral stenosis) and non-rheumatic (older, and without valvular lesion). Of the sixty cases in Table II, fifty were of the rheumatic type (or had exophthalmic goitre), while ten were of the non-rheumatic type (Nos. 9, 16, 23, 31, 36, 41, 43, 51, 52, 58). In No. 29 only was the blood-pressure greatly raised, and here mitral stenosis indicated rheumatic infection of the heart-muscle as the cause of the arrhythmia. In none of the others did the systolic pressure during normal rhythm exceed 170, or the diastolic pressure exceed 90, though systolic readings of 190 and 180 during fibrillation were obtained in two non-rheumatic cases (16, 41) where normal rhythm was not restored.

The association of high blood-pressure with fibrillation is therefore uncommon; and non-rheumatic auricular fibrillation can seldom be explained as being due to hyperpiesis with supervention of auricular fibrillation and consequent fall of blood-pressure. This view is supported by the fact that of the twenty-three cases described in this group only three developed auricular fibrillation before death. (See Table III.) When this association is found, the disorder of rhythm can sometimes be explained by coincident rheumatic heart disease (No. 29, Table II; Case 36, Table III), exophthalmic goitre (No. 53, Table II), or prolonged digitalis administration. It is the rule in failure secondary to high blood-pressure for the normal rhythm of the heart to be retained.

4. Necropsy reports. Case 26. Cardiovascular hypertrophy. Atheromatous obliteration of coronary artery. Old and recent infarction of myocardium. Dense hyaline and slightly calcified fibrous tissue replacing a large part of the posterior wall of the left ventricle. Recent infarction of lower third of interventricular septum. Severe fatty and calcareous atheroma of coronary arteries causing complete closure of the left horizontal at the margo obtusa, and great stenosis of the anterior descending. Hypertrophy of the left ventricle. Valves normal. Moderate general atheroma. Thrombus in right femoral vein. Thrombus in artery to haemorrhagic infarct occupying whole of middle lobe of right lung. Congestion of kidneys, otherwise normal. Microscopic: recent infarction of myocardium.

Case 41. Severe subacute parenchymatous nephritis. Great cardiovascular hypertrophy (heart, 22 oz.). Acute sero-fibrinous pericarditis and pleurisy. Advanced subacute haemorrhagic, lipid, parenchymatous nephritis: 'white

kidney.' Atrophic hydronephrotic left kidney (right kidney, $11\frac{1}{2}$ oz.; left, $1\frac{1}{2}$ oz.). Considerable general atheroma. Congestion and oedema of liver and spleen. Microscopic: right kidney, confirming above.

Case 44. Chronic interstitial nephritis. Cardiovascular hypertrophy. Heart, 24 oz. Great hypertrophy of left ventricle and slight of other chambers. Valves normal. Subacute and chronic fibrotic inflammation of visceral pericardium. Numerous atheromatous buttons in tortuous coronary arteries, and in renal arteries and aorta. Focal microscopic areas of fibrosis in myocardium. Conspicuous arterial hypertrophy, atheroma of arterioles, and considerable cortical fibrosis in kidney (one $4\frac{1}{2}$ oz.). Microscopic: kidney, left ventricle, and commencement and arch of aorta.

TABLE III. Group II. High Blood-pressure.

Case.	Age.	Sex.	History.	Duration of Symptoms.		Dead.	Necropsy.	Pulse-rate.	Extra-systoles.	Pulsus alternans.	Arteries.	Blood-pressure.		Cheyne-Stokes R.	Blood-urea.	Days before death last seen.
				Dyspnoea (years).	Oedema (months).							Syst.	Diast.			
6	57	M	Rh.	2	3	Yes	—	92	++	+	+	230	140	0	51	14
21	44	F	0	1	12	Yes	—	92	0	+	N	190	125	+	0	21
26	64	M	0	$1\frac{1}{2}$	14	Yes	Yes	88	++	++	++	185	130	0	36	1
28	53	M	0	$1\frac{1}{2}$	17	Yes	—	130	+	++	++	240	150	0	51	58
29	52	M	Rh.	1	1	Yes	—	100	+	++	N	215	150	0	29	—
30	59	F	0	—	—	No	—	100	+	0	N	185	100	+	57	6
33	64	F	0	5	33	Yes	—	88	+	+	++	195	110	0	27	—
36	58	M	Rh.	$2\frac{1}{2}$	30	Yes	—	100	+	++	+	180	110	+	45	F.
37	65	M	0	1	2	Yes	—	102	+	++	+	170	110	0	27	28
41	32	M	0	2	6	Yes	Yes	95	0	0	+	200	150	+	38	1
43	53	M	0	4	36	No	—	104	++	++	+	190	130	0	80	30
44	44	M	V. D.	6	1	Yes	Yes	100	0	0	++	190	115	0	50	1
46	39	M	0	$\frac{1}{2}$	1	Yes	Yes	90	0	++	N	170	120	0	0	1
47	62	F	0	4	7	Yes	Yes	90	+	+	+	200	150	+	48	24
50	46	F	0	$3\frac{1}{2}$	42	Yes	Yes	104	+	0	+	210	115	0	28	7
57	60	F	0	$\frac{1}{2}$	4	Yes	Yes	85	0	+	N	215	100	0	38	28
59	56	F	Rh.	2	2	Yes	—	120	0	++	N	225	125	+	184	1
86	69	M	S.	—	—	No	—	104	+	+	N	200	105	0	73	—
89	50	M	V. D.	$1\frac{1}{2}$	10	Yes	Yes	80	+	0	+	190	105	+	57	F.
91	70	M	0	—	—	No	—	68	+	+	N	200	115	0	28	—
88	44	M	0	5	2	Yes	Yes	110	++	+	++	165	130	+	62	1
98	70	M	S.	—	—	No	—	88	++	+	++	195	115	0	78	F.
100	40	M	0	1	6	Yes	—	100	+	+	N	215	125	+	64	1

Case 46. Chronic interstitial nephritis. Cardiovascular hypertrophy. Hypertrophy of left ventricle. Parenchymatous degeneration of myocardium. Slight atheroma. 'Back-pressure' congestion and considerable fibrosis of kidneys; hypertrophy of lobar and arcuate arteries; no hypertrophy nor degeneration of intima of arterioles in kidneys ($12\frac{1}{2}$ oz.). Microscopic: myocardium of left ventricle, and kidneys.

Case 47. Great hypertrophy of all chambers of the heart, especially left ventricle. Oedema and very slight, microscopic, focal, perivascular fibrosis of myocardium; no fatty degeneration of myocardium. Ridge of thickening, apparently degenerated hypertrophy, of anterior layer of posterior cusp of mitral valve.

Case 50. Chronic interstitial nephritis. Cardiovascular hypertrophy. Heart, 21 oz. Great hypertrophy of all chambers. Valves normal. Scattered, small, microscopic foci of fibrosis in myocardium. Moderate general atheroma. Wide coronary arteries. Conspicuous arterial hypertrophy, atheroma of arterioles, and considerable fibrosis of cortex in kidneys (9½ oz.). Areas of confluent 'back-pressure' atrophy in liver. Congestion, hyaline degeneration of arterioles, and slight chronic inflammatory infiltration of spleen. Microscopic: kidney, posterior wall of left ventricle, liver, and spleen, as above. Radial artery; considerable fibrosis of media.

Case 57. Subacute parenchymatous and chronic interstitial nephritis. Cardiovascular hypertrophy. Acute fibrinous pericarditis. Heart, 28 oz. Acute fibrinous pericarditis. Great hypertrophy of left ventricle with slight hypertrophy of other chambers. Very slight, microscopic, focal, perivascular fibrosis of myocardium. No fatty degeneration of myocardium. Moderate atheroma of aorta and coronary arteries. Coronary arteries not stenosed. Congestion of kidneys; acute and subacute parenchymatous and slight chronic interstitial nephritis; hypertrophy of renal arteries, atheroma of a few arterioles. Microscopic: pericardium, myocardium, and kidney.

Case 88. Cardiovascular hypertrophy. Very slight chronic interstitial nephritis. Heart, 22½ oz. Great hypertrophy of left and considerable hypertrophy of right ventricles. Patch of fibrosis in interventricular septum; focal, microscopic areas of perivascular fibrosis in remainder of myocardium. No fatty degeneration of myocardium. Organizing and recent thrombi in right and left ventricles. Valves normal. Congenital abnormality of coronary arteries. Severe atheroma of anterior descending coronary artery. Moderate atheroma of aorta; pit due to rupture of elastic in media of ascending aorta. Hypertrophy of renal arteries; severe fatty atheroma in renal arterioles; a few small fibrotic areas, containing fibrotic glomeruli, in renal cortex. Numerous scarred infarcts in kidneys (11½ oz.). Microscopic: myocardium of both ventricles; anterior descending coronary artery; ascending aorta; kidneys.

Case 89. Considerable chronic interstitial nephritis. Cardiovascular hypertrophy. Heart, 22½ oz. Great hypertrophy of all chambers, particularly left ventricle. Slight, microscopic, perivascular fibrosis of myocardium. Valves normal. Severe general atheroma. Congenital abnormality of left coronary artery. Numerous atheromatous buttons throughout coronary arteries. Hypertrophy of renal arteries, with severe atheroma of arterioles; congestion and considerable reticular fibrosis in cortex of kidneys (14 oz.); focal fatty degeneration, partly anisotropic, in kidneys. Hyaline degeneration of arterioles in congested spleen. Microscopic: myocardium of left ventricle, kidney, spleen, and liver.

Group III. Chronic Pulmonary.

All cases with severe chronic pulmonary disease in which the blood-pressure was within normal limits, and clinical or necropsy evidence of rheumatism or syphilis was absent, have been included in this group.

1. *Clinical features.* The clinical features of the nineteen cases in this group are summarized in Table IV. Seventeen are dead, and necropsies were obtained in eleven. The average age was 51; the youngest was 34, and four were under 40. A rheumatic history was obtained in two. A history of syphilis was never obtained, and though the Wassermann reaction was positive in one (97),

necropsy showed no evidence of syphilis. All had suffered from shortness of breath, 'asthma', or bronchitis for a number of years, some even from childhood. In the seventeen who are dead, the average duration of oedema was only five months. Two are still living, a year after the onset of oedema. Many had systolic murmurs at the apex, but none presented clinical or post-mortem evidence of organic valvular disease. The average pulse-rate was 103; extra-systoles were infrequently observed, and pulsus alternans was found in four only. The arteries were clinically thickened in seven. The highest blood-urea estimation was 85, and no patient exhibited clinical evidence of renal disease. In one alone was Cheyne-Stokes respiration observed. The physical signs in the lungs were variable and depended upon the particular pulmonary lesions, but all exhibited signs of severe chronic emphysema, usually with bronchitis. Some showed slight irregular pyrexia, and many clubbing of the fingers. All failed with progressive oedema and ascites, and venous congestion was invariably pronounced. The suffused cyanotic appearance of these patients, with the prolonged laboured expiration, the rattling chest, and copious expectoration, combined with massive oedema, made a clinical picture almost unmistakable. Auricular fibrillation was never observed during the course of failure.

2. *The cause of failure.* Primary lung disease is known to be a cause of heart failure, and in our cases chronic emphysema with bronchitis, and sometimes pulmonary fibrosis with bronchiectasis, were the commonest lesions. In two, multiple infarction of the lungs from embolic blocking of branches of the pulmonary arteries (from thrombosis in the right auricle) accelerated death. In all there were relative hypertrophy of the right auricle and ventricle, and hypertrophy of the pulmonary arteries and their branches, with atheroma of the intima. These findings support the usual view that there has been a persistently raised pressure in the pulmonary artery to maintain the circulation through the lungs. Failure of the right ventricle secondary to pulmonary disease is in this respect analogous to failure of the left ventricle secondary to increased peripheral resistance in the systemic circuit. In both these conditions the chief cause of the failure is outside the heart and largely mechanical in nature. It is true that in patients with heart failure of this kind foci of chronic infection are present, as the bronchi themselves; but though this may play a part in the production of failure, the necropsy findings indicate that the chief cause of failure is an extra-cardiac one, a view which is confirmed by the fact that, apart from fatty degeneration, the myocardium shows slight, if any, histological change.

3. *The rhythm.* If heart failure in chronic pulmonary disease is determined by an extra-cardiac cause, by analogy with failure secondary to high blood-pressure, we should not expect auricular fibrillation to occur. The heart-muscle is not primarily diseased, it is simply unable to cope with the increased resistance that advanced lung disease entails. This is confirmed by the high proportion of cases in this series in which failure is so explained, and by the fact that in none of them did fibrillation subsequently occur. The majority of older patients with cardiac failure of any kind have some pulmonary symptoms and signs, but these

do not predominate from the first as they do in heart failure secondary to chronic pulmonary disease. Our experience is that in failure due to this cause normal rhythm is preserved.

TABLE IV. *Group III. Chronic Pulmonary.*

Case.	Age.	Sex.	History.	Dyspnoea (years).	Oedema (months).	Dead.	Necropsy.	Pulse-rate.	Extra-systoles.	Pulsus alternans.	Arteries.	Blood-pressure.		Blood-urea.	Days before death last seen.
												Syst.	Diast.		
11	65	F	0	5	1	Yes	Yes	110	0	0	N	140	90	0	1
17	46	M	0	20	10	Yes	—	80	0	0	+	130	70	38	69
19	41	M	0	10	18	Yes	Yes	100	0	0	N	125	80	44	1
31	46	M	0	10	1	Yes	—	105	0	0	N	105	65	0	1
32	52	M	0	20	4	Yes	Yes	104	0	0	N	110	70	51	12
14	70	M	0	10	?	Yes	Yes	90	0	0	N	115	65	27	7
58	67	M	0	5	1	Yes	Yes	110	0	0	N	160	70	0	3
65	38	M	0	5	1	Yes	—	108	+	+	N	115	90	0	1
67	66	M	0	4	1	Yes	—	100	+	+	+	115	70	85	7
61	45	M	0	—	—	—	—	88	0	0	N	125	80	24	—
77	37	F	0	20	3	Yes	Yes	134	0	0	N	120	70	0	19
80	36	M	0	12	1	Yes	Yes	122	0	0	+	125	90	63	14
81	61	F	0	5	6	Yes	Yes	88	0	0	N	135	55	58	17
90	48	M	Rh.	5	?	Yes	—	110	0	+	+	115	85	0	4
93	66	F	0	—	—	—	—	108	0	0	N	130	55	0	—
73	41	F	0	3	14	Yes	Yes	118	+	0	+	125	70	26	18
79	55	M	Rh.	7	11	Yes	Yes	78	0	+	+	110	75	38	30
74	34	M	0	15	1	Yes	—	120	0	0	N	115	80	0	13
97	38	M	0	7	3	Yes	Yes	110	0	0	N	120	95	49	1

4. *Necropsy reports.* Case 11. *Acute and chronic bronchitis and emphysema. Thrombosis of ovarian veins. Pulmonary embolism.* Heart, 15½ oz. Considerable hypertrophy of right, but none of left ventricle. No endocarditis. Moderate atheroma of thoracic aorta, and severe calcareous and fatty atheroma of pulmonary arteries. Chronic emphysema, chronic hypertrophic bronchitis, and slight acute muco-purulent bronchitis in lungs. Recent and organizing infarcts in lungs. Several thrombi in large branches of pulmonary arteries. Microscopic: lung.

Case 19. *Chronic bronchitis and emphysema.* Great hypertrophy of right auricle and ventricle. Slight focal fatty degeneration of right ventricle. Small left auricle and ventricle (L. V. 1 cm., R. V. 0.7 cm. thick). Focal chronic fibrous pericarditis upon right ventricle. Valves normal. Slight atheroma. Coronary arteries normal. Slight chronic interstitial nephritis. Fatty infiltration, central congestion, and slight portal fibrosis in liver. Microscopic: myocardium and pericardium of right ventricle; kidney; liver; spleen.

Case 32. *Chronic emphysema of lungs. Chronic and acute bronchitis. Thrombosis or embolism of pulmonary arteries.* Recent haemorrhagic infarcts in lungs. Slight focal fatty degeneration and conspicuous hypertrophy of right ventricle, which forms apex of heart. Small left ventricle (R. V. 0.65 cm., L. V. 1.1 cm. thick). No ante-mortem thrombus in right side of heart. Avascular thickening of contact layers towards free extremity of cusps of tricuspid valve. Other valves normal. Slight atheroma. Wide coronary arteries. Chronic hypertrophic and focal acute purulent bronchitis, and bronchiolitis. Great emphysema of both lungs. Partly organizing thrombi in many small branches of pulmonary artery throughout both lungs. Ante-mortem thrombus blocking branches of

pulmonary artery in both lower lobes. Recent haemorrhagic infarct in each upper lobe. Congestion and very severe, confluent, central, 'back-pressure' necrosis of liver. Microscopic: tricuspid valve; wall of right ventricle; lower lobe of right and upper lobes of left lung; liver.

Case 14. Great chronic emphysema, and anthracosis of lungs. Slight acute muco-purulent bronchitis; chronic bronchitis and considerable bronchiectasis. Ossification of bronchial cartilages. Chronic inflammation and anthracosis of bronchial glands. Moderate hypertrophy of right ventricle; left ventricle of normal size (R. V. 0.6 cm., L. V. 1.45 cm. thick). No endocarditis. No macroscopic degeneration of muscle of ventricles. Moderate general atheroma. A few fat-flecks in hypertrophied intima of pulmonary arteries. Pleural cavities obliterated by adhesions. Microscopic cysts in capsules of Bowman in kidneys. Microscopic: lungs; left bronchus; gland of tracheal bifurcation; kidney.

Case 58. Chronic emphysema. Purulent bronchitis and slight broncho-pneumonia. Great hypertrophy of right ventricle and auricle, former forming apex of heart (L. V. 1.5 cm., R. V. 0.6 cm. thick). Focal fatty degeneration of endocardial aspect of right, but none of left ventricle. Chronic and subacute ? rheumatic pericarditis, forming large 'milk patch' upon right ventricle. Valves normal. Slight atheroma. Small patches of calcareous atheroma in coronaries. Severe, confluent, central engorgement and necrosis of liver. A few small areas of fibrosis, containing fibrotic glomeruli, in kidneys. Microscopic: right ventricle with pericardium; lung; liver; kidney.

Case 77. Acute and chronic bronchitis and bronchiectasis. Fibrosis of lungs. Heart, 9½ oz. Great hypertrophy of right ventricle. Small left auricle and ventricle. Valves normal. Slight atheroma. Chronic bronchiolitis, bronchiectasis, and great peribronchial interstitial infiltration and fibrosis in lower lobe of right lung. Areas of bronchiectasis in rest of lungs. Hypertrophy of intima of pulmonary arteries. Canalized organized thrombosis of pulmonary arteries in left lower lobe. Severe purulent bronchitis with great congestion of lungs. Microscopic: lower lobes of right and left lungs.

Case 80. Chronic bronchitis and emphysema. Congestion, purulent bronchiolitis and haemorrhage in lower lobes of lungs. Heart, 21½ oz. Great hypertrophy of right ventricle and auricle. No hypertrophy of left ventricle or auricle. Valves normal. Slight atheroma. Coronary arteries normal. Thickened and dilated pulmonary arteries. Congestion and parenchymatous degeneration of kidneys. Microscopic: upper lobe of right and lower lobe of left lung; kidney.

Case 81. Chronic emphysema. Acute purulent and chronic bronchitis. Heart, 15¾ oz. Great hypertrophy of right ventricle. Moderately well developed left ventricle. Valves normal. Ball thrombus in right auricular appendix. Slight general atheroma; slight atheroma of coronaries. Chronic vesicular emphysema; conspicuous thickening of pulmonary arteries and slight chronic hypertrophic inflammation, and acute purulent inflammation of bronchioles. Fatty infiltration of liver. A very few, small, microscopic areas of fibrosis beneath capsules of kidneys. Microscopic: lung; liver; kidney.

Case 73. Chronic emphysema. Early subacute nephritis. Chronic septicaemia. Agonal bacteraemia. Great hypertrophy of right ventricle and auricle. Small left auricle and ventricle (R. V. 0.8 cm., L. V. 1.4 cm. thick). Valves normal. Moderate atheroma. Congestion, very severe albuminous degeneration, anisotropic fat in groups of cortical tubules, perivascular infiltration with plasma cells, hyaline casts, and emboli of Gram-positive cocci, without associated inflammatory

infiltration, in kidneys. Chronic septic spleen: conspicuous perivascular infiltration with plasma cells. Fatty infiltration and areas of 'back-pressure' atrophy in liver. Thrombus in central vein of suprarenal capsule. Microscopic: lung; kidney; spleen; liver; suprarenal capsule.

Case 79. Acute and chronic bronchitis, broncho-pneumonia, bronchiectasis, emphysema, and very severe anthracosis of lungs. Endarteritis obliterans in anthracotic pulmonary nodules. Great hypertrophy of right ventricle forming apex of heart, but none of right auricle. Slight atrophy of left ventricle. Valves normal. Slight atheroma. Pulmonary arteries thickened. Microscopic: right and left lung.

Case 97. Chronic emphysema. Great hypertrophy of right ventricle and less marked of right auricle. Relatively small left ventricle (R. V. 1.0 c.m., L. V. 1.5 cm. thick). Right ventricle forms apex of heart. No fatty degeneration of myocardium. Valves normal. Slight atheroma. Coronaries normal. Great congestion, albuminous degeneration, slight fatty degeneration of several second convoluted tubules and of a few cells of discharging tubules, and fibrosis of a few glomeruli in kidneys. Microscopic: right and left ventricle; kidney.

Group IV. 'Primary Myocardial.'

The diagnosis of 'primary myocardial failure' is usually reached by the uncertain method of excluding other known causes of failure. We have therefore placed in this group those cases in which the systolic blood-pressure was below 165 and the diastolic below 100 mm. of Hg, and evidence (clinical or necropsy) of cardiovascular syphilis, rheumatic endocarditis, or chronic pulmonary disease was absent. Those with a history of syphilis or rheumatism alone have not on that account been excluded.

1. *Clinical features.* The 13 cases falling into this group are summarized in Table V. Eight are dead and necropsies were obtained in four.

2. *The cause of failure.* In those cases of heart failure where no other pathological condition to explain it is clinically apparent, the heart, and especially the heart-muscle, are often assumed to be primarily at fault. But it is well to classify the possible causes of failure in such a case.

(i) *Primary heart failure.* (a) Interference with the blood-supply to the myocardium from atheromatous coronary disease. Ischaemic fibrosis. (b) Primary heart-muscle disease. Chronic non-rheumatic myocarditis or degeneration.

(ii) *Secondary heart failure.* Inability of a normal myocardium to maintain the necessary blood-pressure to meet increased peripheral resistance. Cardio-vascular hypertrophy.

Two cases of this group (2, 68) showed extensive focal fibrosis of the myocardium resulting from obliterative atheromatous or thrombotic coronary disease. Two others (23, 95) had complete heart-block, and though necropsies were not obtained, it is assumed, as syphilis could be excluded, that failure was due to a similar lesion. These four were all over 60 years of age. In only one (Case 2) was the onset of cardiac symptoms sudden and associated with cardiac pain, and

necropsy showed organized thrombosis superimposed on coronary atheroma. In the others the onset of cardiac symptoms was gradual and unaccompanied by pain. In these, perhaps, the occlusion of the coronary arteries occurred slowly, as is suggested by the necropsy findings in Case 68, which showed the coronary occlusion to be due to obliterative atheroma without thrombosis. Two necropsies were obtained in the remaining eight cases (42, 48). During life they were considered to have primary heart disease, for the blood-pressure was low when they were first examined. Necropsy, however, showed predominant left ventricular hypertrophy and systemic vascular hypertrophy with little coronary atheroma and no apparent myocardial disease. They were examples of heart failure secondary to previous high blood-pressure.

We have had difficulty in finding evidence from the literature as to whether the blood-pressure falls in hyperpiesia when the heart fails. Allbutt (2) expresses the view that it may fall somewhat, but rarely to the normal. Fahr (7) believes that the blood-pressure tends to fall in the later stages of hyperpiesis. He cites two cases of heart failure in which the systolic blood-pressure just before death was only 140, though necropsy showed arteriosclerotic kidneys. From this he concludes that the blood-pressure had previously been high. Starling (27), on the other hand, obtained no evidence that in hypertension the blood-pressure ever fell as the heart failed. Batty Shaw (26) has recorded the systolic blood-pressure in 47 cases of hyperpiesia regularly until death, but few of these had such orthopnoea and dropsy as would have led to their inclusion in this series of failure with normal rhythm, or else there were extraneous complications determining death. From his charts it is certain that hypertension often continues unabated until death, if this occurs from uraemia or cerebral haemorrhage. In his few cases where cardiac failure was a feature, the blood-pressure tended to decline, but only during the last few days of life. (*Vide* his Cases 33, 39, 42.)

As our patients were in many different hospitals over a wide area, blood-pressure observations have been infrequent. In Table VI are set out such observations as were made on the cases included in Group II, i. e. patients with severe heart failure and blood-pressures of 160 systolic and 100 diastolic, or over, at the time when they first came under observation, and then during the course of failure. No data are available before the onset of failure. In five (26, 30, 50, 57, 59), the blood-pressure fell to some extent while under observation. Four of these have died, and one (Case 30) is still alive. It is important to note that, according to our arbitrary definition of high blood-pressure, not one of these five would have been included in the high blood-pressure group had they chanced to come first under our observation after the blood-pressure had fallen to the lower levels; they would have been included in this group of primary myocardial failure instead. In nine (21, 28, 36, 41, 43, 47, 88, 89, 100) the blood-pressure was maintained at a high level during progressive failure until death. Three (33, 86, 91) are still alive, with the high blood-pressure persisting.

These observations indicate that while in most cases of failure secondary to high blood-pressure some degree of hypertension is usually maintained, in

a fair proportion the blood-pressure falls to even a normal level. This fact and the pathological findings lead to the conclusion that both cases under discussion (42, 48) are not examples of primary heart disease, but of failure secondary to high blood-pressure, in which the arterial tension fell as the heart continued to fail. Reference has been made to this condition by Donzelot (6) as the 'cœur camouflé' of hyperpietics; and it may explain isolated examples of so-called primary or essential cardiac hypertrophy with failure.

It has thus been possible to reach a definite diagnosis in six of the thirteen cases of this group, which in two is based on the presence of complete heart-block, and in four on the necropsy findings. In four the failure was due to atheromatous coronary disease, and in two it was consequent upon previous high blood-pressure.

Of the seven patients remaining (Table V), four are alive, three are dead (no necropsy). An exact diagnosis is impossible except in Case 70, which was first seen with failure, and a blood-pressure of 150/100. After considerable improvement seven months later, successive blood-pressure readings over a further period of five months were: 190/115, 170/95, 185/110, 155/105. It is evident that here the underlying cause of failure was hyperpiesis.

The remainder were probably either coronary or hyperpietic, maybe both, with the possible exception of Case 25, where the history of several attacks of rheumatism in childhood suggested rheumatic myocardial disease without valvular lesion. This is the only likely example, in the whole group, of failure due to primary heart-muscle disease, and even in this case the blood-pressure twenty months later was 175/90.

No clinical features were found which enabled us to distinguish between the coronary and the hyperpietic cases, for cases of each group conformed to the congestive type of cardiac failure. None of the proven cases of coronary failure gave a history of pain, and they did not show pulsus alternans. Heart failure with normal rhythm without apparent cause is most often due either to (1) hyperpiesis with fall of blood-pressure accompanying failure, or to (2) primary heart failure from coronary atheroma. It is rarely due to chronic inflammatory change directly affecting the heart-muscle (a chronic non-rheumatic myocarditis).

3. *The rhythm.* The relative frequency of failure with normal rhythm and failure with auricular fibrillation in cases of high blood-pressure has already been discussed (see Group II). The incidence of auricular fibrillation in heart failure from non-syphilitic coronary disease alone remains to be considered.

This group contains four cases in which failure was attributable to occlusion of the main coronary arteries. That such cases commonly fail with normal rhythm is suggested by the fact that, in failure due to syphilitic occlusion, normal rhythm is maintained (see Group I). If there is rapid and serious interference with the blood-supply of the ventricular muscle, as may occur in cardiovascular syphilis, or in occlusion of a main coronary by atheroma or thrombosis, the heart is likely to fail and the patient to die before there has been time for auricular fibrillation to develop. Thus both Herrick (11) and Wearn (29)

have published series of cases with coronary occlusion where the heart sometimes became irregular, but merely from extra-systoles. Again, although complete heart-block is so frequently the product of coronary disease, it is uncommon to find it combined with auricular fibrillation. If, however, the changes are more gradual and diffuse, particularly if resident in the finer coronary branches to the auricles, the function of the ventricle is less harshly disturbed and one would imagine that auricular fibrillation will have both the occasion and time to appear. Incidentally it has been recently stated that the coronary branches to the auricles approximate more to end-arteries than those to the ventricles (5). In any case, this may be the explanation of a proportion of cases of non-rheumatic auricular fibrillation. We have already shown that such are not to be regarded as hyperpietics with fall of blood-pressure; and the fact that so many continue in fair health for years makes it improbable that occlusion of the larger vessels is often the pathological basis of the arrhythmia.

TABLE V. *Group IV. 'Primary Myocardial.'*

Case.	Age.	Sex.	History.	Dyspnoea (years).	Oedema (months).	Dead.	Necropsy.	Cardiac Lesions.	Pulse-rate.	Extra-systoles.	Pulsus alternans.	Arteries.	Blood- pressure.		Cheyne-Stokes R.	Blood-urea.	Days before death last seen.
													Syst.	Diast.			
2	65	M	0	1	11	Yes	Yes	0	84	+	0	N	155	100	0	32	6
68	64	M	S	1	8	Yes	Yes	0	85	0	0	N	115	90	+	61	8
23	70	M	0	1½	7	Yes	—	C.H.B.	30	0	0	+	230	85	0	33	28
95	64	M	0	—	—	—	—	C.H.B.	28	0	0	N	165	60	0	43	—
42	61	M	0	2½	18	Yes	Yes	0	112	+	++	N	100	80	0	56	1
48	56	M	0	1½	6	Yes	Yes	0	80	0	0	+	125	80	0	31	1
7	57	F	0	2	3	Yes	—	0	90	0	0	+	135	85	0	49	28
25	43	F	Rh.	—	—	—	—	0	72	0	0	+	130	80	0	39	—
34	63	M	0	1½	3	Yes	—	0	100	0	0	N	140	85	0	53	10
16	63	F	Rh.	—	—	—	—	B.B.L.	85	+	+	N	125	95	0	28	—
82	67	F	0	¼	2	Yes	—	0	104	+	0	+	130	70	0	51	6
70	64	F	Rh.	—	—	—	—	0	90	+	0	+	150	100	0	41	—
49	64	M	S	—	—	—	—	0	72	0	0	+	125	65	0	45	—

4. *Necropsy reports. Case 2. Ischaemic fibrosis of myocardium. Thrombotic and atheromatous occlusion of coronary artery.* Cardiovascular hypertrophy. Heart, 21 oz. Dense white fibrosis of anterior wall and apex of left ventricle, and of anterior two-thirds of the interventricular septum. Considerable hypertrophy of left ventricle. Confluent calcareous atheroma of first 3 cm. of anterior descending coronary artery, with its lumen occupied by organized, canalized thrombus. Numerous fatty and calcareous buttons causing moderate stenosis of lumen of left horizontal coronary artery. Cardiac valves normal. Considerable general atheroma. Purulent bronchitis and oedema of lungs. A few fibrotic glomeruli in kidneys; hypertrophy of media of arteries in kidneys. Microscopic: lower part of anterior wall of left ventricle; upper part of anterior descending coronary artery; kidney.

TABLE VI. *Blood-pressure Observations during the Course of Failure secondary to High Blood-pressure (Group II).*

Case.	Day		1	331	352			
21	Day			190	195			
	B. P.	S.	125	130	died			
		D.						
26	Day		1	22	247	300	442	445
	B. P.	S.	185	140	165	170	140	died
		D.	130	90	110	95	100	
28	Day		1	13	93			
	D. P.	S.	240	240	died			
		D.	150	150				
30	Day		1	231	285	461		
	B. P.	S.	185	170	165	165		
		D.	100	90	80	80		
33	Day		1	133	238	450		
	B. P.	S.	195	210	225	died		
		D.	110	115	135			
36	Day		1	28	50			151
	B. P.	S.	180	196	175	aur.	—	died
		D.	110	115	115	fibr.	—	
41	Day		1	32	39	49	55	129
	B. P.	S.	200	190	190	200	210	230
		D.	150	135	150	150	150	170
								died
43	Day		1	28	55	83	433	463
	B. P.	S.	185	225	205	220	240	died
		D.	130	120	140	140	150	
47	Day		1	21	53	79	103	
	B. P.	S.	200	200	200	200	died	
		D.	150	120	130	135		
50	Day		1	48	108	115		
	B. P.	S.	210	170	170	died		
		D.	135	130	95			
57	Day		1	16	44			
	B. P.	S.	210	195	died			
		D.	100	90				
59	Day		1	12	15	19	22	23
	B. P.	S.	215	160	190	185	170	died
		D.	125	110	115	110	95	
86	Day		1	21	54			
	B. P.	S.	200	195	195			
		D.	105	105	105			
88*	Day		1	10	22	36	60	
	B. P.	S.	165	155	150	155	died	
		D.	130	?	120	120		
89	Day		1	21		—	127	
	B. P.	S.	190	230	aur.	—	died	
		D.	105	130	fibr.			
91	Day		1	21	56	160	340	
	B. P.	S.	200	200	235	240	180	
		D.	115	115	105	110	90	
100	Day		1	4	54	131	148	
	B. P.	S.	215	210	220	210	died	
		D.	125	125	—	150		

* 3 years previously, 210/130; 1 year previously, 190/140.

Case 48. Cardiovascular hypertrophy. Large heart with predominating left ventricular hypertrophy. Aorta smooth. Coronary arteries and cardiac valves normal. Other organs normal.

Case 68. Ischaemic fibrosis of myocardium. Obliterative atheroma of coronary arteries. Heart, 16½ oz. Dilatation but no hypertrophy of left ventricle. Large area of fibrosis affecting the endocardial part of the myocardium of the apex of the left ventricle and of the whole extent of the interventricular septum. Severe atheroma of the coronary arteries. Calcified, fatty, and fibrotic atheroma reducing the lumen of the anterior descending coronary artery to a pin-point. Great stenosis of left horizontal coronary artery. A few atheromatous buttons in commencement of right coronary artery. Severe fatty atheroma of aorta, but no evidence of syphilitic aortitis. Fatty infiltration, and central congestion and atrophy of liver. Congestion, albuminous degeneration, and fatty degeneration of second convoluted tubules in kidneys; a few small areas of ischaemic fibrosis in kidneys; degenerated hypertrophy of intima of arcuate and interlobular vessels. Microscopic: anterior descending coronary artery; commencement of aorta; descending thoracic aorta; liver; kidney.

Case 42. Cardiovascular hypertrophy. Agonal bacteraemia. Heart, 23½ oz. Conspicuous hypertrophy of left and moderate hypertrophy of right ventricle (L. V. 1.8; R. V. 0.53 cm. thick). Microscopic focal areas of fibrosis in and beneath endocardium of right ventricle; fatty degeneration of one or two fibres of myocardium close to endocardium of left ventricle. No stenosis of coronary arteries. Moderate general atheroma. Cocci filling capillaries of glomeruli without any inflammatory reaction, fatty degeneration of second convoluted tubules, fibrosis of a very few glomeruli, hypertrophy of arteries, and post-mortem degeneration of kidneys. Confluent central congestion and atrophy of liver. Slight chronic emphysema of lungs. Microscopic: margo obtusa, interventricular septum and right ventricle; kidney; liver; lung; thymus.

Group V. Rheumatic.

In this group are included those cases with clinical or necropsy evidence of rheumatic endocarditis, even if there was coexistent high blood-pressure. The histories and clinical features are summarized in Table VII. Of the fifteen in the group, all are dead and necropsies were obtained in eleven. A synopsis of individual cases will here be given, for the non-occurrence of auricular fibrillation in rheumatic heart failure is exceptional and has to be discussed.

Case 12. Female, aged 23. Died three months after oedema first appeared. Necropsy: Severe mitral stenosis. Adherent pericardium; chronic fibrotic pericarditis; active, vegetative, and chronic fibro-calcareous rheumatic endocarditis of mitral valve. Active, vegetative, and chronic fibrotic endocarditis of tricuspid and pulmonary valves. Aortic valves normal. Fibrosis and infiltration of mural endocardium of both auricles, greatest and calcified on left. Fibrosis and infiltration of myocardium beneath attachments of affected valves. Slight infiltration of node of Tawara. Great hypertrophy of right auricle and ventricle; small left ventricle. Microscopic: mitral valve; pulmonary valve; pericardium; auricular and ventricular walls; node of Tawara.

Case 60. Female, aged 22. Died two weeks after oedema first appeared. Necropsy: Broncho-pneumonia; infarction of lung; extreme mitral stenosis; active, vegetative, and chronic rheumatic endocarditis of mitral, aortic, and

tricuspid valves. Great hypertrophy of right auricle and ventricle. Ante-mortem thrombus in right auricular appendix. Slight general atheroma; large atheromatous buttons in thick pulmonary arteries. Ante-mortem thrombus in main branches of pulmonary artery to middle lobe and upper part of lower lobe of right lung, with purulent bronchitis, broncho-pneumonia, and consolidation in these areas. Atrophy of right kidney, with calculus in ureter. Hypertrophy and congestion of left kidney. Congestion of spleen. Microscopic: mitral valve; tricuspid valve; middle lobe of right lung; spleen; kidney.

Case 63. Female, aged 28. Pregnant. Died two months after oedema first appeared. *Necropsy:* *Acute sero-fibrino-purulent pleurisy; mitral stenosis; acute and chronic rheumatic endocarditis of mitral and aortic valves.* Calcification of mitral valve. Gelatinous vegetations on posterior cusp of mitral valve and on contact margin of aortic valve. Hydropericardium ($1\frac{1}{2}$ pints). Great dilatation and hypertrophy of left auricle, and to a less extent of right auricle and ventricle. Calcified, fibrotic area in myocardium of left ventricle close to attachment of mitral valve. Severe ? syphilitic, ? rheumatic, chronic inflammation of commencement of aorta. Oedematous lungs. Haemorrhagic infarct in lower lobe of left lung. Severe parenchymatous degeneration of firm 'back-pressure' kidneys. Confluent central engorgement and necrosis of liver. Microscopic: mitral and aortic valves (chronic changes alone present in sections); myocardium of both ventricles; ascending aorta; lung; liver; kidney; spleen.

Case 96. Female, aged 27. Oedema appeared during the last five months of pregnancy; she then gave birth to a healthy child without much aggravation of the failure, but died six weeks later. After digitalis (tinct., drachm i, daily) had been given for twelve days, auricular fibrillation supervened. The Wassermann reaction was found to be positive by one laboratory and negative by another, but there was no evidence of syphilis at necropsy. *Necropsy:* *Acute and chronic rheumatic endocarditis; mitral stenosis; aortic incompetence.* Great cardiac enlargement. Aortic valves thickened, with small vegetations. Mitral stenosis. Recent infarct in lung.

Case 8. Male, aged 34. Died one month after oedema first appeared. *Clinical diagnosis:* *Chronic rheumatic endocarditis, mitral stenosis, and aortic incompetence; infective endocarditis.* There was moderate pyrexia, but no splenic enlargement, no haematuria, no clubbing, and no purpura or other signs characteristic of infective endocarditis. Subsequently, however, streptococci were grown in a blood-culture, making the diagnosis of infective endocarditis almost certain. No necropsy.

Case 38. Male, aged 30. Died seven months after oedema first appeared. *Necropsy:* *Chronic rheumatic endocarditis; aortic incompetence; infective endocarditis.* Heart, 30 oz. Thickening and distortion of aortic cusps causing aortic incompetence. Recent red vegetation on aortic cusp, with adherent thrombus. Aorta and coronaries normal. Spleen enlarged, $12\frac{1}{2}$ oz., with scar of old infarct.

Case 62. Female, aged 40. Died two months after oedema first appeared. Blood-pressure, 225 systolic, 120 diastolic. *Necropsy:* *Cardiovascular hypertrophy; acute and chronic rheumatic endocarditis; mitral stenosis.* Moderate hypertrophy of left and slight hypertrophy of right ventricle. Thickening of cusps of mitral valve and shortening of chordae tendineae, causing stenosis of mitral valve, admitting one finger only. A few tiny vegetations on cusps of mitral and otherwise normal cusps of aortic valves. Coronary arteries normal. Atheroma of arterioles, and slight ischaemic fibrosis in congested, fatty kidneys. Microscopic: mitral valve; fibrotic thickening and vascularization, without active inflammatory reaction; fibrosis of tips of papillary muscles. Kidney.

Case 76. Male, aged 36. Died twelve months after oedema first appeared. *Necropsy:* Chronic, inactive, rheumatic endocarditis of mitral, aortic, and tricuspid valves; mitral stenosis. Hypertrophy and great dilatation of left auricle; slight hypertrophy of left ventricle; dilatation and hypertrophy of right auricle; great dilatation and hypertrophy of right ventricle. Microscopic perivascular fibrosis in myocardium. *Mitral stenosis:* opening 3×0.4 cm. area of very irregular, ulcerated, calcareous atheroma covering almost the whole of the contact margin of the aortic cusp and the medial half of the contact margin of posterior cusp of greatly thickened and retracted mitral valve. Slight thickening of aortic and tricuspid valves. Fibrous pleural adhesions over whole of both lungs. Haemosiderosis, anthracosis, congestion and emphysema of lungs. Considerable chronic interstitial nephritis, apparently ischaemic. Extensive central 'back-pressure' atrophy in liver. Microscopic: mitral valve; tricuspid valve; myocardium of right ventricle; lung; kidney; liver; spleen.

Case 66. Female, aged 29. Died two months after oedema first appeared, and four months after her only confinement. *Necropsy:* Chronic rheumatic endocarditis of aortic and mitral valves; aortic incompetence; mitral stenosis. Heart, $18\frac{1}{2}$ oz. Hypertrophy of left ventricle; slight hypertrophy of other chambers. Perivascular and larger focal, microscopic area of fibrosis in myocardium. Patchy fatty degeneration of myocardium. Slight infiltration and very slight fibrosis of bundle of Stanley Kent. Considerable fibrous thickening and fusion of mitral cusps. Fibrous thickening and great contraction and retraction of aortic cusps. No vegetations. Slight atheroma. Coronaries normal. Two recent haemorrhagic infarcts in lungs. Fatty degeneration of kidneys. Microscopic: aortic, mitral, and tricuspid valves; myocardium of left ventricle; kidney.

Case 51. Male, aged 43. Died two weeks after oedema first appeared. *Necropsy:* Chronic rheumatic endocarditis; aortic stenosis and incompetence. Heart, 26 oz. Hypertrophy of left ventricle. Thickening and calcification of adherent aortic cusps, causing aortic stenosis and incompetence. Other valves normal. No signs of acute endocarditis. Aorta and coronary arteries normal. Kidneys normal.

Case 84. Male, aged 39. Died two months after oedema first appeared. *Clinical diagnosis:* Chronic rheumatic endocarditis; aortic incompetence. No necropsy.

Case 71. Female, aged 39. Oedema appeared during her last pregnancy, and she died ten months after its first appearance. *Clinical diagnosis:* Chronic rheumatic endocarditis; mitral stenosis. No necropsy.

Case 94. Female, aged 52. Died one month after oedema first appeared. *Clinical diagnosis:* Chronic rheumatic endocarditis; mitral stenosis; aortic incompetence; broncho-pneumonia. No necropsy.

Case 18. Female, aged 40. Oedema three days before admission; two days later pulmonary infarction with aggravation of failure. Improvement. Treated as out-patient. Two years later, after prolonged treatment with digitalis, auricular fibrillation. Death, twenty-four months after oedema first appeared. *Necropsy:* Chronic rheumatic endocarditis of aortic, mitral, and tricuspid valves; mitral stenosis. Great thickening, retraction and nodular calcareous atheroma of cusps of mitral valve; mitral orifice 1 cm. in diameter. Nodular calcareous atheroma in thickened cusps of aortic valve. Thickening and retraction of chordae tendineae, and thickening of contact margin of tricuspid valve. Dilata-

tion of left auricle, right ventricle, and right auricle; hypertrophy of myocardium, greatest in right ventricle. Moderate general atheroma; fatty flecks in intima of coronary arteries. Recent, and slightly older, haemorrhagic infarcts in considerably indurated lungs. A few fibrotic glomeruli and small areas of fibrosis in kidneys; congestion, severe albuminous and hyaline droplet degeneration, and focal areas of anisotropic fatty degeneration, in congested "back-pressure" kidney. Confluent central congestion and central fatty degeneration in liver. Congestion of spleen. Microscopic: aortic cusp of mitral valve; right posterior cusp of aortic valve; lung; right and left kidneys; liver; spleen.

Case 75. Died two months after onset of oedema. Blood-pressure, 185 systolic, 90 diastolic. *Chronic rheumatic endocarditis and? myocarditis. Cardiovascular hypertrophy.* Heart, 19 oz. Considerable hypertrophy of left ventricle. Slight fibrous thickening of contact margin of mitral and of competent aortic valves; thickening and shortening of chordae tendineae of mitral valve. Perivascular and larger areas of fibrosis, associated with infiltration with lymphocytes, endothelial cells, and fat-granule cells and, occasionally, neutrophil leucocytes, in myocardium of left ventricle; fatty degeneration of a very few muscle-fibres in left ventricle. Slight atheroma. A few fatty buttons in coronary arteries, but no appreciable stenosis. Hypertrophy and slight fibrosis of media of radial artery. Congestion, parenchymatous degeneration, hyaline casts, fibrosis of a very few glomeruli, and conspicuous hypertrophy of arteries in congested spleen. Central congestion and atrophy of liver. Microscopic: margo obtusa of heart; liver; spleen; kidney; radial artery.

The rhythm. Auricular fibrillation is well known to be the common associate of a failing chronic rheumatic heart. As rheumatism is such a frequent cause of heart failure, but the cause in only fifteen of our 100 cases with normal rhythm, it follows that the large majority of rheumatic hearts must fail with auricular fibrillation. If this is the rule, our fifteen rheumatic cases are exceptions, and demand some explanation. This is frequently not far to seek in terms of what we have already learned as to the causation of failure with normal rhythm. Thus, of the eleven cases on which necropsies were obtained, four had acute rheumatic endocarditis superimposed on chronic rheumatic heart disease and died within two or three months of the onset of oedema. One other died of superimposed infective endocarditis. In these acute conditions, as opposed to chronic rheumatic heart disease, normal rhythm is known usually to persist. In one (62) the blood-pressure during life was 225/120, and necropsy showed systemic cardiovascular hypertrophy in addition to mitral stenosis and acute endocarditis. In another (75) the blood-pressure during life was 185/90. Necropsy showed systemic cardiovascular hypertrophy in addition to chronic rheumatic endocarditis. One other (18) did subsequently develop auricular fibrillation.

Of the four cases without necropsy, one died of infective endocarditis (positive blood culture), one failed after pregnancy, and one died of bronchopneumonia.

There thus remain three cases with necropsy and one case without necropsy in which the non-occurrence of auricular fibrillation cannot be explained. But three of these all had aortic incompetence. We have already seen that cases of

syphilitic aortic incompetence fail with normal rhythm. Perhaps the lesion is a greater mechanical disadvantage than mitral stenosis, and like other mechanical factors favours a premature failure with normal rhythm.

Some have emphasized the mechanical stress on the auricle in mitral stenosis as a factor in the production of fibrillation. But in failure secondary to chronic pulmonary disease, as in congenital malformations of the heart (13), the rhythm is normal. Yet here the strain on the auricle, as evidenced by its hypertrophy, must be to some extent comparable. The essential lesion responsible for fibrillation in chronic rheumatic heart disease, whether mitral stenosis is present or not, is chronic rheumatic myocarditis.

TABLE VII. *Group V. Rheumatic.*

Case.	Age.	Sex.	History.	Dyspnoea (years).	Oedema (months).	Dead.	Necropsy.	Valvular Lesion.	Pulse-rate.	Extra-systoles.	Arteries.	Blood-pressure.		Blood-urea.	Days before death last seen.
												Syst.	Diast.		
12	23	F	Rh.	4	3	Yes	Yes	M. S.	112	0	—	105	85	54	5
60	22	F	0	3	$\frac{1}{2}$	Yes	Yes	M. S.	110	0	N	—	—	—	1
63	28	M	Rh.	4	2	Yes	Yes	M. S.	112	0	N	120	—	—	1
96	27	F	Rh.	7	5	Yes	Yes	M. S., A. I.	120	0	N	140	90	78	F.
8	34	M	Rh.	1	1	Yes	—	M. S., A. I.	120	0	N	155	50	—	1
38	30	M	Rh.	2 $\frac{1}{2}$	7	Yes	Yes	A. I.	105	0	+	150	—	80	1
62	40	F	Rh.	$\frac{1}{2}$	2	Yes	Yes	M. S.	110	+	N	225	120	69	12
76	36	M	Rh.	5	12	Yes	Yes	M. S., A. I.	130	0	N	110	85	29	1
66	29	F	Rh.	3	2	Yes	Yes	M. S., A. I.	100	0	N	135	55	51	8
51	43	M	0	$\frac{1}{2}$	$\frac{1}{2}$	Yes	Yes	A. S., A. I.	110	0	+	105	60	—	1
84	39	M	Rh.	1 $\frac{1}{2}$	2	Yes	—	A. I.	120	0	—	—	—	—	12
71	39	F	0	9	10	Yes	—	M. S.	116	+	N	115	75	—	19
94	52	M	Rh.	1	1	Yes	—	M. S., A. I.	80	++	N	120	45	48	1
18	40	F	Rh.	4	24	Yes	Yes	M. S., A. I.	72	0	N	145	90	35	F.
75	58	M	Rh.	1 $\frac{1}{2}$	2	Yes	Yes	M. S.	105	0	+	185	90	53	1

Group VI. Unclassified.

The remaining nine cases are here included. In three of them necropsies were made, but these did not justify their inclusion in previous groups. For this reason, and to save space, the full necropsy reports are omitted.

Case 39. Male, aged 45. Shortness of breath since childhood. Oedema for seven months before death. No history of rheumatism or syphilis; Wassermann reaction positive. Great cardiac enlargement with loud systolic murmur at all areas. Gross oedema and ascites. Pulse-rate, 68; normal rhythm with frequent ventricular extra-systoles; no pulsus alternans. Arteries not thickened. Blood-pressure, 130 and 85. Blood-urea, 41. Tinct. of digitalis, B. P., drachm i daily, caused the oedema to disappear, but on the twelfth day auricular fibrillation supervened preceded by auricular flutter. Subsequently, oedema returned, and he died some months later. *Necropsy:* Congenital pulmonary stenosis; patent interventricular septum; syphilitic aortitis.

Case 87. Male, aged 53. No history of rheumatism. Wassermann reaction negative a fortnight before death; positive in blood *post mortem*. Duration of

shortness of breath and oedema to death, five months and six weeks respectively. Aortic systolic and diastolic murmurs. Pulse-rate, 94; normal rhythm. Arteries thickened. Blood-pressure, 130 and 70. Moderate oedema. Albuminuria. Blood-urea, 96. Died three weeks later, normal rhythm persisting. *Necropsy: Healed calcareous, rheumatic, or subacute malignant endocarditis; aortic stenosis and incompetence.*

Case 53. Female, aged 54. No rheumatic history. Shortness of breath and oedema for two months before death. Wassermann reaction weakly positive. No valvular lesion. Pulse, 110; normal rhythm; no pulsus alternans. Arteries not thickened. Blood-pressure, 110 and 55. Moderate oedema. Fundi normal. Blood-urea, 19. Extreme anaemia, but blood-film showed no excess of white cells nor alteration in form of red cells. Died five days later, with normal rhythm. *Necropsy: ? Septicaemia and severe secondary anaemia.*

In the remaining six cases, now summarized, necropsies were not obtained and there was insufficient evidence during life on which to base a differential diagnosis among the possible causes of failure.

Case 52. Male, aged 68. No rheumatic history. Chronic bronchitis ten years. Duration of oedema to death, six weeks. Chronic bronchitis and emphysema with extreme venous congestion. Wassermann reaction positive. Pulse-rate, 70; normal rhythm; no pulsus alternans. Arteries thickened. Blood-pressure, 165 and 80. Heart-sounds inaudible. Moderate oedema and ascites. Blood-urea, 45. Fundi normal. Died ten days later. The failure may have been due to chronic pulmonary disease, or to cardiovascular syphilis, or to both.

Case 27. Male, aged 43. No history of syphilis or rheumatism. Shortness of breath and oedema for two years before death. Wassermann reaction found positive by one laboratory and negative by three others at the same time (no treatment). Moderate pyrexia. No valvular disease. Left bundle-branch lesion (electro-cardiogram). Pulse, 100; normal rhythm; no pulsus alternans. Blood-pressure, 160 and 130. Spleen not palpable. Moderate oedema. Blood-urea, 28. Fundi normal. Under digitalis administration (tincture, drachm i daily) the oedema disappeared and he had a transient attack of auricular fibrillation lasting two days; normal rhythm returned spontaneously although digitalis was being given as before. He died nine months later. It was impossible to decide whether the failure was due to cardiovascular syphilis, high blood-pressure, coronary atheroma, or infective endocarditis.

Case 72. Male, aged 70. Shortness of breath and oedema for nine and six months respectively. Doubtful rheumatic history. Wassermann reaction negative. Aortic incompetence. Pulse-rate, 80; normal rhythm; no pulsus alternans. Blood-pressure, 120 and 65. Arteries tortuous. Chronic bronchitis and emphysema. Moderate oedema. Blood-urea, 28. Died six months later; no necropsy. It was impossible to decide whether the aortic incompetence was rheumatic, syphilitic, or atheromatous, or whether the failure was due to coronary disease.

Case 83. Female, aged 49. No rheumatic history. Wassermann reaction negative. No valvular lesions. Pulse-rate, 108; normal rhythm; no pulsus alternans. Arteries not thickened. Blood-pressure, 140 and 105. Emphysema with bronchitis. Gross oedema. Blood-urea, 32. Fundi normal. Death presumed (untraced). As the blood-pressure in hospital six months before was noted as 180 systolic and 140 diastolic, it is likely that failure was secondary to previous high blood-pressure.

Case 1. Female, aged 47. No rheumatic history. Symptoms dated from a mastoid operation three years previously. Shortness of breath for three years and oedema for one year. Wassermann reaction negative. Aortic incompetence. Irregular pyrexia. Pulse, 100; normal rhythm; no pulsus alternans. Arteries not unduly thickened. Blood-pressure, 135 and 70. Palpable spleen. Slight oedema. No clubbing. Leucopenia with 84 per cent. of neutrophils. Blood culture sterile. Digitalis caused an irregular rhythm due to heart-block. She died five months later. Probable diagnosis, chronic rheumatic endocarditis complicated by infective endocarditis.

Case 92. Male, aged 54. Chronic bronchitis and emphysema. No valvular lesion. Pulse, 108; normal rhythm. No extra-systoles, no pulsus alternans. Arteries thickened. Blood-pressure, 125 and 60. Moderate oedema. Blood-urea, 48. Wassermann reaction negative. Eleven months later, the blood-pressure was found to be 175 and 110, and radioscapy showed enlargement of the heart to the left. At first this was considered an example of failure secondary to chronic pulmonary disease, but later as secondary to high blood-pressure.

The Clinical Varieties of Heart Failure with Normal Rhythm.

One hundred unselected cases of severe heart failure with normal rhythm, between the ages of 20 and 70 years, have been investigated. Those with recognized infective endocarditis, and those with acute infections such as pneumonia or diphtheria, alone have been excluded. The pathological basis of the failure proved to be as follows:

Cardiovascular hypertrophy—		
with high blood-pressure	(23 cases of Group II)	
without high blood-pressure	(3 cases of Group IV)	26
Cardiovascular syphilis	(20 cases of Group I)	20
Chronic pulmonary disease	(19 cases of Group III)	19
Chronic rheumatic heart disease	(7 cases of Group V)	7
Acute on chronic rheumatic heart disease	(4 cases of Group V)	4
Coronary atheroma	(4 cases of Group IV)	4
Congenital heart disease *	(1 case of Group VI)	1
Rheumatic heart disease and infective endocarditis	(2 cases of Group V)	2
Cardiovascular hypertrophy (high blood-pressure) and cardiovascular syphilis	(1 case of Group I)	1
Cardiovascular hypertrophy (high blood-pressure) and rheumatic heart disease	(2 cases of Group V)	2
No cause apparent clinically and no necropsy (probably coronary atheroma or cardiovascular hypertrophy)	(6 cases of Group IV)	6
Multiple possible causes of failure (no necropsy)	(6 cases of Group VI)	6
Necropsy inconclusive	(2 cases of Group VI)	2
		<hr/> 100

* Necropsy showed slight syphilitic aortitis in addition.

The three common lesions in congestive heart failure *with normal rhythm* are therefore cardiovascular hypertrophy (high blood-pressure), cardiovascular syphilis, and chronic pulmonary disease. Rheumatic heart disease and coronary atheroma are relatively infrequent. The commonest condition of all, accounting for more than 25 per cent. of our cases, is cardiovascular hypertrophy with high blood-pressure. It is often assumed that failure with auricular fibrillation is also commonly due to high blood-pressure, and that many non-rheumatic cases

are thus explained. We dissent from this view and have already furnished evidence to the contrary. Fahr (7) has emphasized the frequent association of hypertension with heart failure without regard to the presence or absence of auricular fibrillation. But in reaching so high an estimate as 75 per cent. of all cases of chronic 'heart-muscle disease' he included many cases of cardiac enlargement and non-rheumatic auricular fibrillation in which the occurrence of high blood-pressure was assumed.

Cardiovascular syphilis was responsible for failure in at least 20 per cent. of our cases. That proven cases of syphilis may yield negative Wassermann reactions has already been shown, so that syphilis may possibly have been a factor in others besides the twenty-two in which it was certainly present. Thus, out of the remaining seventy-eight with no accepted evidence of it, either clinical or post-mortem, a definite history of syphilis was obtained in four. The Wassermann reaction was positive in four others; three of them positive (one laboratory) and negative (another) in blood simultaneously collected.

Aortic incompetence with heart failure and a normal rhythm is oftener due to syphilis than to rheumatism. Atheromatous aortic incompetence was never seen, with the possible exception of Case 72, who reached our upper age limit of 70.

Two only of our patients were obese, and in both the failure was attributable to high blood-pressure. No evidence has been obtained to show that fatty degeneration or fatty infiltration alone is a sufficient cause of heart failure with normal rhythm.

One patient (Case 39) had congenital pulmonary stenosis and failed with normal rhythm. In this connexion we agree with Laubry, who states that he has never seen auricular fibrillation in failure due to congenital morbus cordis (13).

The clinical features of congestive failure with normal rhythm are almost identical with those of failure with auricular fibrillation. Further, the general appearance was much the same in all our groups, whether valvular disease was present or not, and whether the failure was primarily cardiac or secondary to an extra-cardiac cause, with the exception of the pulmonary group. The absence of any high grade of simple tachycardia in spite of extreme heart failure is noticeable; and it can only be in isolated instances that a high cardiac rate is a serious factor in the production of failure with normal rhythm. The average pulse-rate in the four chief groups proved to be:

Group I.	Cardiovascular syphilis	92
" II.	High blood-pressure	97
" III.	Chronic pulmonary	103
" IV.	Rheumatic	105

Pulsus alternans was recorded in the radial tracings as follows:

	No. of Cases.	Pulsus alternans.	%.
Cardiovascular syphilis	20	4	20
High blood-pressure	25	19	76
Chronic pulmonary	19	4	21
Coronary atheroma (excluding heart-block)	2	0	—
Rheumatic heart disease	11	0	—

The incidence of pulsus alternans proves to be much greater in failure secondary to high blood-pressure than in primary heart failure. If failure in high blood-pressure is a secondary phenomenon, pulsus alternans is an indication of cardiac exhaustion rather than of cardiac disease itself.

Cheyne-Stokes respiration was observed as follows :

	No. of Cases.	Cheyne-Stokes Respiration.
Cardiovascular syphilis	20	9
High blood-pressure	25	9
Chronic pulmonary	19	1
Coronary atheroma	4	1
Rheumatic heart disease	11	0

Cheyne-Stokes respiration is thus shown to be infrequent only in failure with normal rhythm occurring in chronic pulmonary disease and in rheumatic heart disease.

The Prognosis in Heart Failure with Normal Rhythm.

A patient with rheumatic heart disease commonly continues in fair health until the onset of auricular fibrillation. Then, within a few days, all the signs of failure supervene, to disappear if digitalis controls the ventricular rate or if by any means normal rhythm returns. Auricular fibrillation and its associated tachycardia may determine failure long before the heart-muscle disease by itself would do. The prognosis when fibrillation first occurs is therefore often good in so far as the failure is due to this arrhythmia and a tachycardia which can be controlled. But in course of time quinidine will no longer prevent the recurrence of fibrillation, and digitalis no longer postpone failure. Failure is now due chiefly to the progress of the myocardial disease, and in a minor degree to the disorder of rhythm. The prognosis in heart failure with normal rhythm is, generally speaking, worse than in failure with auricular fibrillation. And for this there are two reasons. (1) Heart failure with normal rhythm indicates a more advanced degree of myocardial insufficiency than does a corresponding degree of failure with auricular fibrillation, where a part is due to the disorder of rhythm and the consequent ventricular tachycardia. (2) For heart failure with auricular fibrillation we have at our disposal either digitalis or quinidine. Apart from syphilis, for heart failure with normal rhythm we have no specific treatment. Digitalis does benefit some of these patients to a large extent, but the results so obtained are seldom comparable with those obtained in auricular fibrillation.

In the types of heart failure described, the average duration of life from the first appearance of oedema was as follows :

Group.	Total Cases.	Number Dead.	Average Duration of Oedema before Death (months).	Number still alive (1-3 yrs.).
I. Cardiovascular syphilis	21	18	10	3
II. High blood-pressure	23	18	11	5
III. Chronic pulmonary	19	17	5	2
IV. Primary myocardial	13	8	7	5
V. Rheumatic	15	15	6	0
VI. Unclassified	9	8	8	1
	100	84	8	16

Of our 100 cases, 84 are dead and 16 are still alive one to three years after the onset of oedema. In those who have died the average duration of oedema was eight months. Once oedema is seen in a patient suffering from heart failure with normal rhythm the prognosis is serious, particularly when the heart fails from chronic lung disease or rheumatic heart disease. Besides the septic absorption from infected bronchi, inability to circulate the blood through the lungs must constitute a more serious disorder of function than failure to circulate the blood through the periphery. In rheumatic patients failing with normal rhythm, death occurs much earlier than in such patients failing with auricular fibrillation, often because of a superadded active rheumatic infection or a complicating infective endocarditis.

Summary and Conclusions.

1. One hundred unselected cases of *severe* congestive heart failure with normal cardiac rhythm between the ages of 20 and 70 are described. Recognized infective endocarditis and heart failure in the acute infections such as pneumonia have alone been excluded.

Failure with normal rhythm is far less frequent than failure with auricular fibrillation. This series has only been obtained by searching several large hospitals over a period of two years.

Eighty-four have died and necropsies were obtained in forty-eight.

2. The pathological condition to which failure was attributable proved to be cardiovascular hypertrophy (high blood-pressure) in 26, cardiovascular syphilis in 20, chronic pulmonary disease in 19, chronic rheumatic heart disease in 7, acute on chronic rheumatic endocarditis in 4, atheromatous coronary occlusion in 4, and congenital morbus cordis in 1.

Apart from these, in two the failure was due to chronic rheumatic heart disease and high blood-pressure, in two to chronic rheumatic heart disease complicated by infective endocarditis, and in one to high blood-pressure complicated by cardiovascular syphilis. In the remaining fourteen the pathological basis of failure was uncertain.

3. Two undoubted aetiological factors in the production of auricular fibrillation are chronic rheumatic myocarditis and the toxæmia of exophthalmic goitre; the full administration of digitalis may occasionally produce it. This is con-

firmed by the fact that, considering the frequency of rheumatism as a cause of heart failure, in only four of our series was the failure with normal rhythm attributable to uncomplicated chronic rheumatic heart disease and not once to exophthalmic goitre.

Only seven cases in the whole series subsequently acquired auricular fibrillation: two of them had chronic rheumatic heart disease; in one it was attributable to past rheumatic infection, and in three apparently to the heavy administration of digitalis.

Auricular fibrillation with heart failure in these conditions is a late result of chronic inflammation of the myocardium, or of a toxin acting specifically upon it—a chronic affection of the heart-muscle itself.

4. It is acknowledged that normal rhythm usually persists in heart failure due to acute infections of the heart itself, such as rheumatic carditis, infective endocarditis, and diphtheria.

Evidence is adduced showing that normal rhythm likewise persists in heart failure due to cardiovascular hypertrophy (high blood-pressure), chronic pulmonary disease, syphilitic aortic and coronary disease, and atheromatous occlusion of main coronary arteries, as well as to congenital malformations. In these conditions the heart-muscle is not primarily diseased.

5. Tabular evidence is given proving that in hyperpiesia (cardiovascular hypertrophy) the blood-pressure sometimes falls to normal during the progress of failure.

Cases with no apparent clinical cause of failure are described and classified as 'primary myocardial'. Necropsy showed that in some of these the failure was due to previous high blood-pressure (systemic cardiovascular hypertrophy) and in others to atheromatous occlusion of main coronary arteries. In none of them was it due to chronic myocardial inflammation or degeneration. No example in the whole series was seen of failure with normal rhythm from non-rheumatic primary myocardial disease or degeneration.

6. Auricular fibrillation in patients without evidence of rheumatic heart disease is sometimes attributed to previous high blood-pressure, with the assumption that the arterial tension has fallen with the onset of the disorder of rhythm. But an analysis of a separate series of patients with auricular fibrillation and a ventricular rate controlled by digitalis shows that the systolic blood-pressure is not appreciably changed by restoration of normal rhythm with quinidine. We have also seen that in failure secondary to high blood-pressure normal rhythm persists. 'Non-rheumatic' auricular fibrillation therefore cannot often be attributed to hyperpiesia.

These facts, and those in Groups 3 and 5 above, as well as the expectation of life, lead us to suggest that the pathological basis underlying non-rheumatic auricular fibrillation is likely to be found in a generalized change in the auricular muscle, such as might result from chronic inflammation, toxæmia, or diffuse coronary sclerosis.

7. The collected evidence shows that the circumstances which determine

whether auricular fibrillation shall accompany failure, or whether normal rhythm shall persist, are as follows :

(a) When failure is largely determined by gradually developing *mechanical* factors, and the auricular muscle is not primarily diseased, e.g. uncomplicated high blood-pressure, chronic pulmonary disease, congenital malformations, and gross aortic incompetence, normal rhythm persists.

(b) When failure is due to *acute inflammation* of the heart-muscle (acute rheumatic carditis, infective endocarditis), normal rhythm persists. But when it depends upon a *chronic inflammation* (chronic rheumatic myocarditis), or the effect of specific toxæmias (exophthalmic goitre, cf. also digitalis), auricular fibrillation is likely to supervene.

(c) When failure is due to interference with the *blood-supply* of the heart, the rate and extent of this process and the region affected are all of importance. If the lesion is focal, as when the main coronary branches are obstructed, the heart is likely to fail with normal rhythm. But it is suggested that if the lesion is diffuse and the process more gradual, so that the smaller branches of the coronary arteries to the auricle are affected, the heart is likely to fail with auricular fibrillation.

8. The presence or absence of fibrillation is of value in the differential diagnosis of the pathological basis of a case of heart failure. Further it may be of assistance in assessing the relative importance of the different causes at work in a complicated case. Thus if normal rhythm is found where auricular fibrillation would be expected e.g. in chronic rheumatic heart disease, suspicion should be aroused that the failure is due to some complication, such as infective endocarditis, high blood-pressure, or chronic pulmonary disease. In the absence of these, persistence of normal rhythm suggests that the failure is due more to the mechanical embarrassment of the valvular lesions than to the associated myocardial disease.

On the other hand, failure with auricular fibrillation where normal rhythm would be expected, suggests that the failure is not entirely due to mechanical factors, nor to gross interference with the blood-supply of the ventricle alone, but partly to a myocardium weakened by chronic inflammation, primary degeneration, toxæmia, or generalized coronary sclerosis.

9. The frequency of syphilis as a cause of severe heart failure with normal rhythm is notable. Syphilis may be the cause, and a history of it actually obtained, even though the Wassermann reaction is negative.

Syphilis and rheumatism are the only common causes of aortic incompetence and heart failure with normal rhythm below 70 years of age. Only one case is recorded in which the condition was probably due to atheroma.

10. All the types of failure described, including those with aortic incompetence, died with progressive orthopnoea, oedema, and ascites, much like cases of failure with auricular fibrillation. Failure secondary to chronic pulmonary disease is characterized (as might be expected) by an extreme degree of cyanosis and venous congestion.

The pulse-rate was seldom high (average, 100), so that tachycardia is not an important factor in this form of failure. In high blood-pressure a special feature is *pulsus alternans*, often associated with extra-systoles, a combination which may closely simulate the pulse of auricular fibrillation. *Pulsus alternans* was recorded in 76 per cent. of the high blood-pressure cases, but in only 21 per cent. of those with chronic pulmonary disease, and 20 per cent. of those with cardiovascular syphilis. It may therefore be more representative of myocardial exhaustion than disease.

11. Of the cases with high blood-pressure, few presented clinical evidence of renal disease. Necropsies showed that a correspondingly small minority had severe primary nephritis, though many had some degree of associated chronic interstitial nephritis.

The majority of cases of primary nephritis die of uraemia or some other complication, but rarely of cardiac failure. On the other hand, while many hyperpetics, with or without associated renal change, die of cerebral haemorrhage, a fair proportion die of congestive cardiac failure (*hypertensive heart failure*).

12. The average duration of life from the onset of oedema in the eighty-four cases which have died during the three years covered by the investigation was only eight months.

The prognosis is least favourable in the rheumatic cases, where an unsuspected acute infection is often present, and in cases failing secondary to chronic lung disease.

The prognosis in failure with normal rhythm is less favourable than in the corresponding degree of failure with auricular fibrillation. In the latter the failure is in part due to the disorder of rhythm and consequent ventricular tachycardia, one or both of which can receive adequate treatment, whereas in failure with normal rhythm the cause (often extra-cardiac) has by itself led to failure for the relief of which no specific therapy is available, unless antisypilitic.

It is a pleasure to record our indebtedness to Drs. W. Brander, A. Chilcott, T. Evans, J. C. Muir, R. D. O'Leary, C. Spurrell, W. R. M. Turtle, J. I. P. Wilson, and W. J. Woodyatt, Medical Superintendents of London Poor Law Hospitals, who kindly allowed us free access to their wards and so made the collection of the series of cases possible, and also afforded us facilities for post-mortem examinations. We wish to thank Dr. W. W. Woods, working in Professor Turnbull's laboratory, for his considerable task of making the detailed examination of all our necropsy material, and Professor Turnbull for the abridged pathological reports which appear in the text. We are also grateful to Dr. Charles Miller and Professor Arthur Ellis, Directors of the Medical Unit, for admitting suitable cases to their wards, and to Dr. John Grimshaw for assistance with the text.

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A CASE OF MALIGNANT CHANGE DEVELOPING IN A TUMOUR OF THE RECTO-GENITAL POUCH ASSOCIATED WITH DIFFUSE INFILTRATION OF THE LUNGS AND INTENSE ERYTHRAEMIA¹

By STANLEY BARNES, A. P. THOMSON, AND F. W. M. LAMB

With Plate 17

THIS case was recently reported to the Meeting of the Association of Physicians (May, 1925), and is now put on record on account of its extreme rarity. Indeed we can find no published case in which the clinical course of the disease had presented the same group of symptoms, nor in which the anatomical findings have been of this character. Erythraemia of intense degree without splenic enlargement is rare, but that it should prove in this case to be due to a diffuse growth scattered throughout the lung alveoli, and containing unstriped muscle-tissue, and that the primary growth should be a tumour of the recto-genital pouch which had been sarcomatous, is a combination of facts so rare that we cannot expect to see its parallel.

Case Record.

Apart from measles and whooping cough as a child the patient, who was under the care of Dr. W. J. Hirst, had always had perfect health. Her family history was good and was clear of tuberculosis.

By profession she was a school teacher, and led an active and energetic life; she was keen on games and played tennis and hockey well. Menstruation was normal. In 1923, when she was 27 years old, she decided that she would take a course of physical training to fit herself for the position of games mistress. It was during this period of rather strenuous exertion that the first symptoms of her fatal illness appeared. At the end of a swimming race in which she had taken part she noticed that she was extremely short of breath, and also that she was very blue. These symptoms were so striking that they attracted general attention at the time, and, although she made light of the matter, she was eventually persuaded to give up her idea of becoming a games mistress and to return to ordinary teaching in the belief that her heart had been strained.

Nine months later, on March 18, 1924, she was first seen by one of us (A. P. T.) and then complained of three things: (1) Shortness of breath on exertion. (2) A sense of fatigue which was marked particularly in the morning.

¹ Received August 29, 1925.

She said that she enjoyed nothing more than lying in bed until midday, whereas previously she had been unable to stay at rest after 7 a.m. (3) Loss of weight, which in the course of 9 months had amounted to 10 lb. She weighed 9 st. 7 lb. in June 1923; when her first symptoms appeared she weighed 10 st. 3 lb.

She did not then mention cyanosis (though there is a note that she was blue after the swimming race), and it is unlikely that it was present at the time, for she was sent for advice as a 'cardiac' case, and cyanosis was certainly looked for.

On examination the heart, the blood-vessels, and the blood-pressure were normal. The percussion note at the right apex appeared slightly impaired and there was some retraction above the right clavicle; some fine crepitations were found at the apex of the left lower lobe which did not clear on coughing. In the absence of all other abnormal physical signs it was thought that her symptoms might be due to pulmonary tuberculosis. She was sent to bed for a fortnight so that her resting temperature might be carefully recorded. When seen again at the end of that time the physical signs were unchanged and one examination of the sputum had shown no tubercle bacilli. The temperature had remained steadily normal, but she had lost another 2 lb. in weight. Dr. Harold Black then X-rayed her chest and found a little dimming in the 2nd and 3rd right interspace. She was advised to go to Switzerland, and she started within a few days. On arriving at a sanatorium she was accepted as an early case of pulmonary tuberculosis, and the Medical Superintendent wrote to say that he thought that she would do well. Shortly afterwards, however, a medical friend with whom she was walking noticed that the patient became extraordinarily cyanosed and that 'her face seen against the snow seemed almost black'. This observation was readily confirmed and she was recommended to return home. On her way back she saw Dr. Morley Fletcher, who made the suggestion that she might have polycythaemia vera and had a blood count done, with the following result:

22.7.24.	Red blood corpuscles	6,830,000
	White blood cells	8,800
	Haemoglobin	83 per cent.

A differential count of the white cells was normal, as was the film. She returned to her work during September and October, but was then compelled to give up owing to her increasing distress.

She was seen again in consultation (by A. P. T.) on November 5, 1924. The most striking feature then was the extreme cyanosis. As she walked into the room her face was a purplish black and she was very distressed. Sitting still in front of a fire she recovered an almost natural colour, but the hands remained blue; the slightest movement, as in undressing, caused the cyanosis to appear. She had lost nearly another stone in weight and was now only 8 st. 9 lb. There were still some crepitations at the apex of the left lower lobe, but no impairment of the percussion note was obvious. The heart seemed sound, the spleen was not enlarged.

In view of the varying character of the cyanosis, and of its dark hue, it was difficult to believe that the condition was a primary polycythaemia vera, particularly in the absence of any palpable enlargement of the spleen. A reasonable diagnosis was not made, and the only advice possible was the inadequate suggestion that treatment had better be symptomatic in the shape of applications of X-rays to the long bones. Not unnaturally the patient went to another physician, who supported the hypothesis of polycythaemia and had another blood count done, which corresponded closely with that of July with the exception that the haemoglobin was found to be 102 per cent. During December she got steadily worse and suddenly became desperately ill.

Dr. W. H. Wynn saw her in consultation and found her breathing extremely distressed and the cyanosis very marked. Only a limited examination was possible. There were scattered râles in both lungs, and despite the fact that her

recorded temperature was normal he considered the condition was most probably acute military tuberculosis.

During the next few days she grew gradually worse, the dyspnoea in particular becoming intense. At this stage she also complained of some left costal pain, and when seen by another of us (S. B.) she was in a pitiable condition. She was found sitting up in bed with all extraordinary muscles of respiration in full action in an endeavour to get her breath. The trunk was bent sharply to the left side and any attempt to sit upright produced great distress, whilst lying down was out of the question. Only the most superficial of examinations was possible, but it was found that some dullness was present, extending into the left axilla and merging into the cardiac dullness in front. No breath sounds could be heard here, and vocal fremitus was absent, so that it was assumed that fluid was present. The heart sounds were extremely feeble, especially at the apex. The conclusion reached was that the effusion was probably pleural, but possibly pericardial; and that it was a sequence to the chill contracted ten days before when walking out in bitterly cold weather.

She was given cardiac stimulants and arrangements were made for her admission to the General Hospital, Birmingham, if she recovered sufficiently to make it reasonable to move her. This became possible on January 31, 1925, when the further history was obtained that ten days before admission she had had violent retching but had not vomited. The retching had increased her respiratory distress, but she had had no pain, only a sense of tightness and oppression in the left chest. There was no cough, and she said that there had never been any. The only pain that she had suffered was a transient stab in the left chest at the onset of the acute phase of her illness in the preceding December.

On admission she had pronounced orthopnoea and was very blue. Physical examination revealed no other abnormality. A blood count on 8.2.25 showed the red cells to be 11,000,000 per c.mm. By February 15 they had risen to 13,500,000. The Wassermann reaction was negative.

On February 15 it was possible to examine her much more easily, as the dyspnoea, though still severe, had greatly moderated; it was even possible to get the chest radiographed with the patient erect. It then became clear that the effusion previously noted was pleural and not pericardial; and ten days later about two pints of cream-coloured fluid were aspirated from the left chest. Subsequent examination of the fluid showed no tubercle bacilli and that the majority of the cells present were lymphocytes (91 per cent.): it was later shown that this fluid had the characters of chyle.

An X-ray examination of the chest after the aspiration showed some displacement of the heart to the right and a small fluid shadow at the left base. There was no material improvement in the dyspnoea or cyanosis after the aspiration.

By the beginning of March it was necessary to use oxygen to relieve her distress, and the cyanosis slightly diminished while she was taking it. A little later oedema of the chest wall appeared on the left side and also in the lumbar region: at no time previous to this had she had any oedema. On 18.3.25 signs of free fluid in the abdomen were detected; respiration was extremely laboured and accompanied by recession of the lower thorax during inspiration: the physical signs in the chest were the same as after the aspiration, and the heart, as always, appeared normal.

By 4.4.25 the abdomen was acutely distended by fluid and there was oedema of the abdominal and chest walls. There were now occasional spasms of coughing, but no sputum was forthcoming. There was no pain.

A blood count showed that there were 7,500,000 red cells per c.mm. and 9,400 whites. The film was normal. Presumably this reduction of the total number of red cells was due to the fact that she had had regular oxygen inhalations for a month—over 120 oxygen cylinders were used for this purpose in four weeks.

From this point the patient went rapidly downhill; wasting of the limbs became very marked, and the ascites and pleural effusion on the left side steadily increased and were associated with much oedema of the chest wall and the left arm, and also, to a less degree, in the legs.

She died on 19.4.25; the pulse remained regular and of good volume to the end, and the heart sounds were normal.

The urine was examined several times and was found to be normal; the temperature was occasionally raised to 99° (once to 100° F.), but was consistently normal for the greater part of the last three months of her life.

The post-mortem was made on the day after death (by F. W. M. L.).

The body was that of a well-developed and fairly well nourished young woman, with considerable ascites. The fluid from the abdomen amounted to about four pints, and was turbid, colourless, and consisted of an emulsion of fat droplets. The condition was, in fact, one of chylous ascites.

The left pleural cavity contained 3,500 c.c. of similar fluid, in which masses of gelatinous material were found.

The left lung was completely collapsed.

The right lung was not collapsed, and air could be driven with ease from one part to another, both in the lung substance and under the pleura. On section both lungs presented a curious resemblance to rather coarse rubber sponges. The organs were riddled with holes of various sizes, while the intervening strands of tissue were extremely friable, breaking down under the slightest pressure. The change was general in distribution, and, as the examination was made within a few hours of the death of the patient, post-mortem changes were not at all advanced.

The heart weighed 250 gm. and was normal in appearance. There was no hypertrophy of the right ventricle, and the ductus arteriosus and foramen ovale were closed. The pulmonary artery was normal.

The spleen weighed 70 gm. It was distinctly atrophic, but otherwise normal.

The liver (1,200 gm.) and *kidneys* (320 gm.) were also normal.

The pelvic organs. In Douglas's pouch, just to the left of the middle line, there was a soft yellow mass of tissue resembling a caseous focus. It was poorly defined, roughly triangular or T-shaped, and not more than $\frac{3}{4}$ inch in its longest diameter. It looked as if it had burst through into the peritoneum from the underlying connective tissue. No macroscopic connexion could be traced between this structure and the tube, ovary, uterus, rectum, or bladder, and there was no evidence of tuberculosis in any of these organs.

The lymph glands of the aortic chain were enlarged to 4 or 5 times their normal size, and were of deep red colour and soft consistence. On section they were rough and dry-looking and friable. The terms of consent to the post-mortem made it impossible to examine the brain, spinal cord, and the limb bones.

Histological examination. The first section examined was taken from the soft yellow growth in the pouch of Douglas.

The greater part of this section was occupied by a vascular growth composed of spindle-shaped cells with rod-like nuclei and eosinophil cytoplasm, arranged in irregular bundles. The appearance was that of a sarcoma arising in smooth muscle. The tumour was infiltrating the surrounding tissues very diffusely, and showed a tendency to break up into small vascular tufts with a papilliform arrangement. In the rest of the section four gland-like spaces were seen, lined with a columnar epithelium like that of the endometrium, and these spaces were partly enclosed by strands of apparently normal uterine muscle. This part of the section had the usual characters of an adenomyoma of the recto-genital space. In one area a transition could be seen between the apparently normal muscle and the sarcomatous growth. Some blood-vessels and lymphatics also contained fragments of the growth.

Section of gland from the aortic chain of lymph glands. The capsule of the gland could still be identified, but the whole of the lymphoid tissue was replaced by a tissue closely resembling irregular bundles of smooth muscle, cut in various planes. The resemblance to unstriated muscle in this section was closer than in the last, and the sarcomatous character was less obvious, but the nuclei were more numerous and larger than those of normal muscle, and were irregular in size and shape. Here, as elsewhere, the growth was very vascular.

Section of the lung. Under a low-power lens the texture of the lung substance was seen to be much coarser than usual. This was partly due to thickening of the alveolar walls, and partly to rupture of some of them, with consequent emphysema. The usual pattern of the lung was destroyed by a very diffuse infiltration of atypical muscle-fibres, which were passing both along the alveolar walls and through the alveoli. This infiltration was associated with an abundance of thin-walled capillaries, full of blood. The sarcoma had not formed nodular metastases, but was invading the lung in delicate, irregular strands, and some of the alveoli could be seen with their walls almost completely surrounded by these fibres. Haemorrhages and large phagocytes laden with blood pigment were visible in many alveoli. Thrombosis was seen in some of the vessels, with the early changes of organization.

(Macroscopically several small thrombosed vessels could be seen on the cut surface of the lung, but there was no disease of any of the large or medium-sized pulmonary vessels.)

It is our opinion that the primary source of this diffuse sarcomatous spread was the adenomyoma in the pouch of Douglas. Careful search was made for other possible source, but none was found.

Discussion.

From the clinical standpoint the record of the case shows the extreme difficulty of diagnosis. There were never any menstrual abnormalities to suggest a pelvic examination in a young unmarried woman, and the rectum in November, 1924, five months before her death, showed nothing abnormal.

From the pathological findings it is clear that the cyanosis was due to obstruction to the oxidation of blood in the lungs by the interposition of a layer of sarcomatous cells between the alveolar epithelium and the pulmonary capillaries. The fact that Professor Haswell Wilson postulated a condition of this type before the sections were examined is worthy of record. The free blood-supply to the tumour cells accounts for the lack of any obstruction to the pulmonary circulation and for the absence of any cardiac hypertrophy despite the development of the marked emphysema. Pressure on the thoracic duct by metastatic deposits in glands accounts for the chylous effusions in the abdomen and in the left pleural cavity. During life many possibilities were considered. Early on, tuberculosis appeared probable; at the post-mortem a fibrous patch at the right apex was found which had resulted from the occlusion of a small artery, and it was this lesion, presumably, which gave rise to the signs suggestive of tubercular infiltration in March, 1924. With the onset of severe dyspnoea and extreme cyanosis, polycythaemia vera, a congenital heart defect, Pick's disease, Ayerza's syndrome, and malignant growth of the mediastinum or lung were all suggested. The varying character and dark hue of the cyanosis, which was

always increased by effort, and the absence of any enlargement of the spleen made polycythaemia very unlikely. It seems to us that this case is opposed to the view that the enlargement of the spleen in polycythaemia vera is merely secondary to the erythraemia and is not to be regarded as an essential feature of the disease, for *post mortem* in our patient the spleen was atrophic and the erythraemia had been intense and of long duration.

Repeated X-ray examinations of the chest supported the opinion reached on physical examination that there was no affection of the heart, pericardium, or great vessels (as in Ayerza's syndrome) which could account for the condition; nor was there any evidence of tumour.

The most important practical conclusion seems to be that this case shows definitely that tumours of the recto-genital pouch may become malignant, and that when they are discovered they should be removed completely wherever possible: we stress this point, for we understand that partial removal of these tumours where they have infiltrated widely is largely practised.

Certain points of pathological interest merit attention: (1) The sarcomatous character of the malignant change. (2) The mode of extension of the growth by permeation of the retroperitoneal lymphatics, leading eventually to the production of chylous ascites and pleurisy. (3) The curious diffuse invasion of the lungs.

A discussion of the nature and origin of adenomyomata would obviously be out of place in this communication. The literature is extensive and controversial, and most of it is admirably summarized in Cuthbert Lockyer's *System of Gynaecology*.

Malignancy is extremely rare in adenomyomata, and some have disputed its occurrence. Lockyer is more cautious, and quotes several cases in which carcinomatous changes have been found in the glandular elements of the tumour. This possibility has naturally attracted most attention, as the epithelium is highly specialized and is also known to be definitely invasive. It is widely recognized, of course, that the adenoma or 'endometrioma' of the recto-genital space may be an invasive tumour, extending into surrounding tissues (as, for instance, the rectal wall), but usually pursuing a characteristically benign course. Were this not so, as Lockyer remarks, 'how frequently such carcinomata would occur!' In our case is evident the still rarer occurrence of a sarcoma quite clearly arising from the muscular elements of the growth.

Three examples of this condition, quoted by Lockyer, are on record, none of which has more than a superficial resemblance to the one here described. The literature of sarcoma arising in myomata is more extensive, and the frequency of its occurrence is usually estimated at from 1 to 2 per cent. of all uterine myomata.

Different types of myosarcoma of the uterus are recognized, such as the malignant leiomyoma, the histological characters of which are supposed to be practically identical with those of a benign leiomyoma, and the definite sarcoma, in which the cells present the atypical characters of sarcoma.

As already mentioned, the microscopic characters of the tumour in our case vary in different situations; the section of the gland closely resembles normal smooth muscle, while the growth in Douglas's pouch is frankly sarcomatous, and its muscular origin is not nearly so obvious. Again, in the lung, the structure of the tumour is very like that of smooth muscle.

In regard to the last point, the diffuse permeation of the lung by sarcomatous muscle, it may be stated that the method of invasion was probably not embolic, at least by the blood-stream, otherwise some appearance of nodular metastases would surely have been seen. Diffuse lymphatic permeation of the lung by carcinoma is recognized, but is always associated with the appearance of some nodules of growth, and the pleura is usually the part involved. In this case the vascularity of the growth would give it a dark colour and thus prevent its macroscopic recognition. So little, however, was the condition suspected, from naked-eye inspection, that we think it possible that cases of this kind may have been missed from lack of histological examination.

DESCRIPTION OF FIGURES.

PLATE 17, FIG. 1. Section of the tumour in the recto-genital space, showing the sarcomatous change in the muscle of the adenomyoma. $\times 100$.

FIG. 2. Section of one of the infiltrated lymph glands, showing replacement of all lymphoid tissue by myosarcoma. $\times 100$.

FIG. 3. Section of the lung. $\times 300$. An alveolus is seen in which are several large phagocytes containing blood pigment. Strands of myosarcoma, passing along the alveolar walls, separate adjacent alveoli.

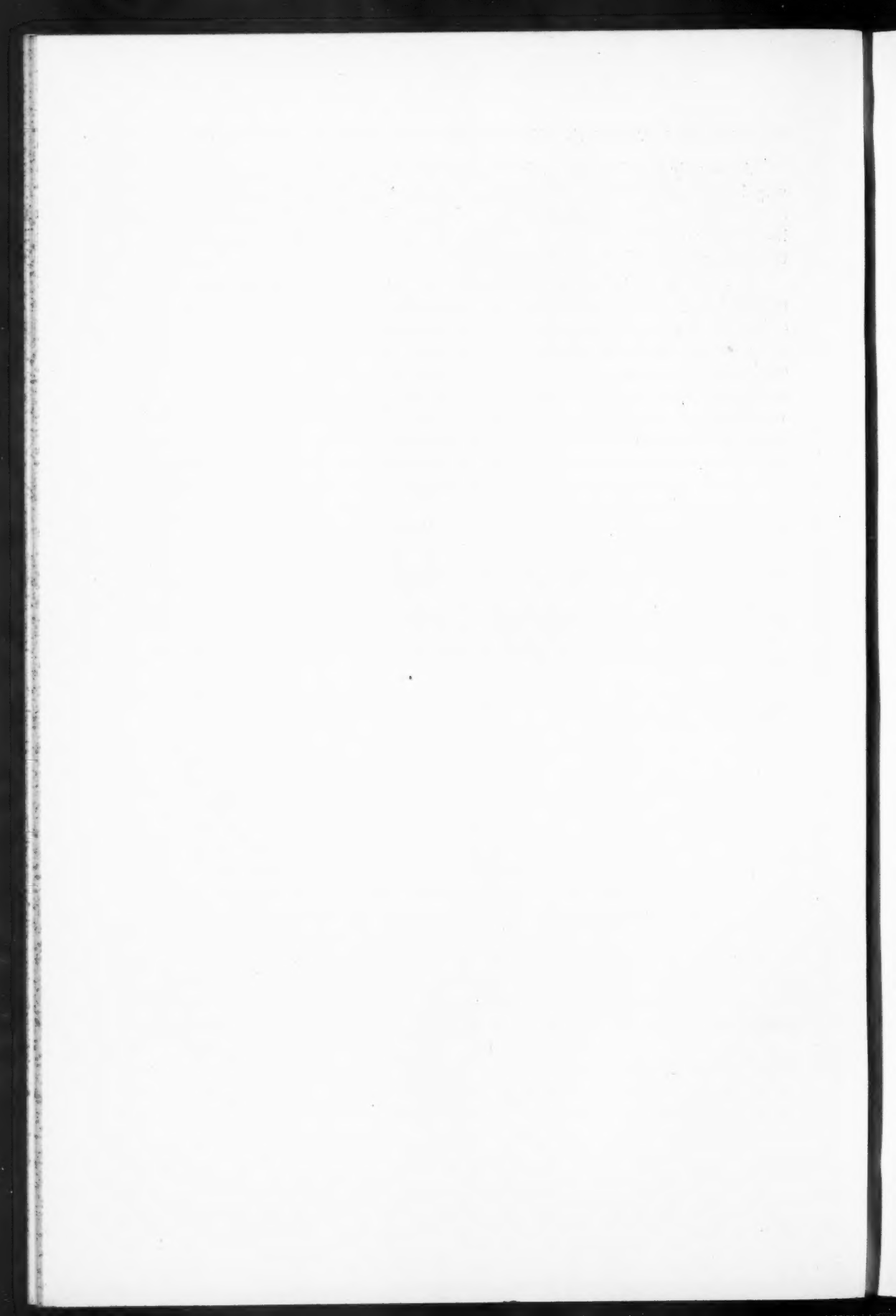


FIG. 1



FIG. 2

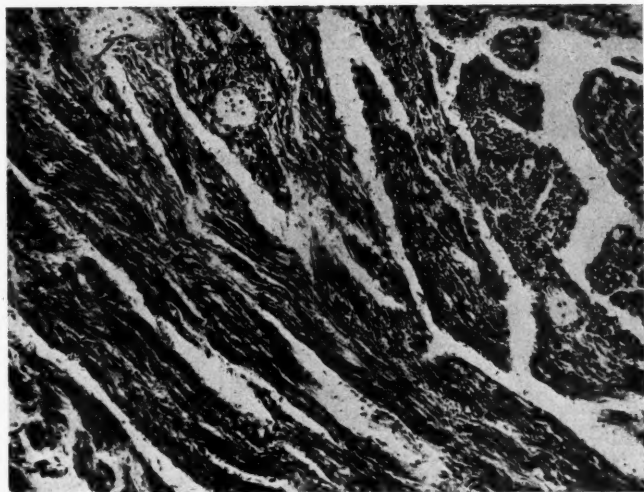
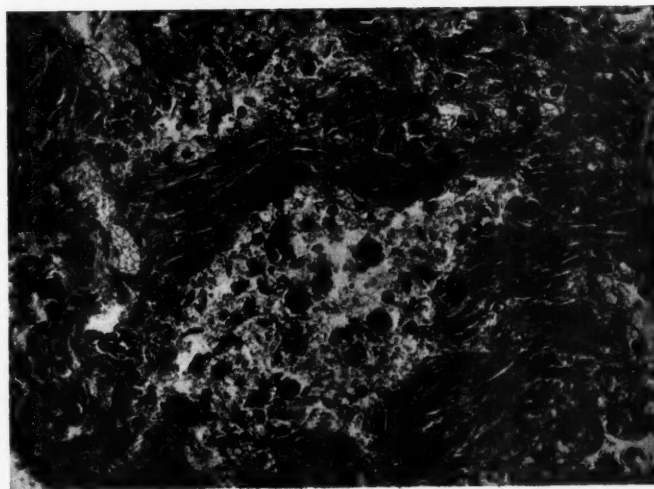


FIG. 3





THE BLOOD-FATS IN DIABETES MELLITUS IN RELATION TO TREATMENT¹

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AN excess of fat is found in the blood in a number of pathological conditions — prolonged under-nutrition, pernicious and secondary anaemias, icterus, more especially that due to obstruction, certain of the nephritides, phosphorus, alcohol, or chloroform poisoning, and as the result of such poisons as pyrocin, pyrogallol, sod. glycocholate, and phenyl-hydrazine. It is, however, much more common in diabetes mellitus, although the extent of the increase may vary greatly from case to case. In very extreme cases the figures may be colossal, Klemperer finding in one case as much as 26 per cent. of fat. More commonly the increase is not so great, the figures varying from 0.8 per cent. to 2.0 per cent. or perhaps 3.0 per cent. at the outside. In the figures recorded in this paper, the term 'total fat' includes the total fatty acid and cholesterol, the total fatty acids including those in combination in the lecithin and in the cholesterol esters, and the fat proper of the blood, the normal being taken as 290 to 420 mg. per cent. total fatty acid, 190 to 250 mg. per cent. cholesterol, or 480 to 670 mg. per cent. total fat (Bloor (1)). When there is a marked increase it is generally visible to the naked eye as a milkiness of the serum, or it may be as a definite layer of fat separating out when the blood is allowed to stand. With smaller quantities the serum or plasma may be quite clear. The visibility or otherwise of the fat is not a function of the amount of fat present, but rather an index of the stability of the condition in which the blood-fat is circulating. The increase in fat content is most marked in the plasma, the fat content of the cells remaining more nearly constant. Beumer and Burger (2) give the following figures for the amount of fat in the ether extract of red cells—0.52 per cent., 0.61 per cent., 0.44 per cent., and 0.52 per cent., in four cases of diabetes; while the ether extract of the blood-serum of these same cases contained, respectively, 0.71 per cent., 2.76 per cent., 0.97 per cent., and 3.33 per cent. of fat. The variations in fatty acid content of the corpuscles as shown by these figures are therefore much less marked than those found in the blood-serum. Similarly, Bloor (3) found that even although all the lipoids in the blood were increased in diabetes, the composition of the corpuscles remains so nearly constant as to be disregarded.

¹ Received September 1, 1924.

On a level with this observation is the fact that even in alimentary lipaemia following the ingestion of fat the changes are most marked in the plasma (Gade (4)), the increase in fatty acids involving the blood-plasma, while the fatty acid content of the corpuscles remains practically at the fasting level.

After the ingestion of fat in the normal organism there is generally an increase in the fatty acids of the blood, the extent and time of onset of which seem to vary considerably. As a rule, the increase in fatty acid content occurs first, and is followed by an increase in the lecithin content, more especially that of the corpuscles. Finally, the cholesterol content may also rise, although this latter increase may not always be observed, since it occurs so late (Iscovesco (5)). These increases observed in alimentary lipaemia have several points in common with the diabetic lipaemia. In a small series of cases, Bloor (6) found that during the development of diabetic lipaemia the fatty acid fraction of the blood lipoids increased first, then the lecithin fraction, and finally the cholesterol, and, as the condition improved, the various fractions decreased in the same order. The later work of Gray (7), on a more extensive series of cases, showed, however, that the relationships described by Bloor did not hold absolutely and that the relative proportions between the various constituents might be altered. Such findings are not surprising, in view of the numerous factors influencing the blood lipoids, and which may be acting in any one case.

Factors influencing the Blood Lipoids in Alimentary Lipaemia.

The type of fat may have some influence on the extent and on the time of onset of the lipaemia. Working with normal dogs, Bang (8) found that butter did not always cause a increase, whereas olive oil always brought about an increase in the fatty acids of the blood. He therefore suggested that the use of olive oil was preferable in experiments on alimentary lipaemia. This variability in response to different fats recalls the varying response to the ingestion of different sugars found by Folin and Berglund (9). When carbohydrate is given along with fat the extent of the lipaemia is greatly modified (Bang (8), Gade (4)), while the addition of protein may cause much greater variations in the fatty acid fractions than would occur after the ingestion of fat alone. Indeed, the influence of protein may not disappear for twelve hours (Sakai (10)). The reasons for these effects are obscure. The improbable suggestion of the participation of the central nervous system put forward by Bønninger and Daddy may be dismissed in virtue of its extreme improbability; but since the blood-fat represents the balance between the amount of fat which the liver is called on to deal with and the amount which may be passing to the tissues for storage or metabolism, it may be surmised that these varying results are an expression of the close relationships between the metabolic processes of the common food-stuffs. Their ultimate significance awaits future investigation.

Other Factors influencing the Blood-fat Level.

When glucose is given to the normal animal it tends at first to lower the blood-fat, affecting mainly the cholesterol, with later a rise resulting from an increase in the fatty acid fraction. This lowering of the cholesterol is also to be observed during the early phases of the absorption of glucose in the human diabetic. Labbé and Theodoresco (11) state that olive oil in some cases may temporarily lower the blood-sugar, while protein has little effect—an observation also made by Folin and Berglund (9), which gives additional evidence of the close relationship between carbohydrate and fat metabolism. Another sugar, laevulose, has been found, in the diabetic at least, to cause a rise in the fatty acids in the blood about six hours after its ingestion. The general metabolic level of the patient has also an important bearing on the blood-fats; Epstein and Lande (12) have shown that the blood cholesterol bears practically an inverse relationship to the basal metabolism, being raised when the basal metabolism is low, and low when the basal metabolism is high. This has been further amplified by the work of Bing and Heckscher (13), who have noted that in hyperthyroid conditions the fatty acid content of the blood is low, while in cases of endocrine deficiency it may be raised, and that in these latter cases the giving of thyroid extract may lower a previously high fatty acid content. Other pathological conditions may also alter the blood-fat level (*vide supra*). The influence of age is not so definite; Bing and Heckscher state that the fatty acids are often low in children and young adults, but the series of cases reported by Bang (14) did not show such a definite influence. C. J. and M. Parhon (15) describe an increase in the blood cholesterol in old age. This may be due simply to the lowering of metabolism that occurs at such a time. Menstruation and pregnancy both raise the blood cholesterol (Shiskin (16)). The presence or absence of acidosis has little influence on the blood-fat; Mansfeld (17) failed to produce lipaemia by the administration of acids to experimental animals. Even in diabetic acidosis one need not necessarily find a high blood-fat.

The Diabetic Lipaemia.

Ebstein's theory that the excess of fat arises from a fatty degeneration of the tissues (18) may be dismissed, there being no facts to support it. The excess of fat in the blood, then, must come either from the fat of the diet or else from the fat of the tissues which may have been remobilized into the circulation for transport elsewhere. Bloor's description of the diabetic lipaemia shows that in its development it may be closely analogous to alimentary lipaemia, except that the changes may be more permanent, but may revert to normal under treatment. Within three or four days of total extirpation of the pancreas there may be a very marked increase in the blood-fats, every element being involved (Seo (19)). But it must be remembered that total extirpation of the pancreas is not strictly

comparable with the average case of human diabetes where there is generally some partially functioning remnant of the pancreas left even in the most severe cases. Allen (20) showed that feeding with excess of fat will greatly increase the blood-fat in partially depancreatized dogs. Further, there are cases of extremely emaciated diabetics who could hardly supply fat from their tissues to cause the extreme lipaemia which they may present. Extreme figures for the blood lipoids are often associated with excessive indulgence in fat in a diabetic who has been told simply to curtail his carbohydrate and has been given no definite instructions as to the amount of fat suitable for him (Murray Lyon (21)). This was a more prominent feature of the earlier types of diabetic treatment when the danger of excess fat in the diet was not adequately realized. The lipaemia observed in phosphorus poisoning, in contrast, probably belongs to the type due to an excess of fat brought from the tissues to the blood-stream. That the food fat has an important bearing on the diabetic lipaemia is well illustrated by the following experiment by Bloor and Gilette (22). They removed enough of the pancreas in two dogs to cause diabetes, and found that after such an operation there resulted a much slower accumulation of fat in the blood-stream and a slower removal of fat from the plasma than when a normal amount of pancreas was present. This showed that the diabetic animal might not be able to use fat as well as the normal animal. Now, in diabetes the diet of the patient can only contain a limited amount of carbohydrate, the amount of which depends on the patient's tolerance, and, as a result, the rest of the diet has to be made up of protein and fat, which in themselves tend to cause greater variations in the blood-fats than would occur under a diet of equal caloric value with a larger proportion of carbohydrate. Thus in the diabetic under treatment the conditions are more favourable for some increase in the blood-fats than in the normal individual with full carbohydrate tolerance. In view of the newer methods of dieting with proper regard to the balance between the ketogenic and anti-ketogenic factors in the diet and also of the introduction of insulin into the treatment of the disease, it seemed of interest to determine what changes the blood-fats might undergo during hospital treatment.

Clinical Features of the Cases recorded, &c.

This includes a record of thirteen cases of diabetes, ten female cases and three male cases, one of which was atypical (Case IV). They were all treated with insulin except Cases III and IV; their ages ranged from thirty to sixty-eight years.

Case I. Jane D., aged 57, housekeeper, first admitted 20.10.22. Her diabetes started in 1914. Signs of circulatory disturbance necessitated the removal of the right great toe, 28.11.22. No familial or hereditary history of diabetes. The patient was stout and the abdomen well covered with subcutaneous fat. Discharged 14.12.22. Readmitted 12.1.23. Discharge and pain in the second toe of the right foot. Toe amputated. Discharged 26.2.23. Readmitted 6.2.24. Pain and redness in the left great toe for one month. No

history of accident. 11.3.24, toe removed under local anaesthesia. Discharged 21.4.24.

TABLE I.
Fasting Blood Chemistry of Case I.

Date.	Blood-sugar.* Mg. %.	Total Fat.† Mg. %.	Cholesterol.† Mg. %.
11.2.24	190	708	234
18.2.24	308	805	202
25.2.24	285	954	238
3.3.24	328	996	259
10.3.24	235	811	221
17.3.24	200	1239	199
24.3.24	317	1327	292
31.3.24	267	1086	347
7.4.24	174	771	187
14.4.24	285	1195	228
21.4.24	211	988	267

* Blood-sugar. Benedict picrate method.

† Total fat and cholesterol (Blood).

TABLE II.
Average Daily Diet of Case I.

Date.	COH. Grm.	Pr. Grm.	Fat. Grm.	G:FA.	Calories.	Insulin Units.
6.2.24-10.2.24	22	29	46	1.02	618	—
11.2.24-17.2.24	61	59	150	1.47	1833	—
18.2.24-24.2.24	71	61	177	1.51	2139	9
25.2.24- 2.3.24	65	62	167	1.52	2010	21
3.3.24- 9.3.24	77	69	186	1.47	2245	34
10.3.24-16.3.24	62	53	147	1.33	1783	24
17.3.24-23.3.24	66	63	168	1.51	2033	12
24.3.24-30.3.24	69	65	150	1.35	2094	16
31.3.24- 6.4.24	73	68	184	1.49	2218	25
7.4.24-13.4.24	75	68	198	1.45	2295	25
14.4.24-20.4.24	81	72	201	1.53	2424	25
21.4.24	81	72	200	1.53	2424	25

During her last stay in hospital, the period of these observations, her weight remained about 7 per cent. above the normal standard.² Her weight when first admitted was similar, while during her second stay in hospital it was markedly sub-standard. Tables I and II give the details of this patient's fasting blood chemistry during her third stay in the wards and her average daily diet in that same period. They are represented graphically in Fig. 1. No definite relationship could be established between the blood-sugar, total fat, cholesterol, and the diet, nor did there appear to be any detectable connexion between the dosage of insulin and the height of the blood-fats.

Case II. Mrs. C., aged 61. Admitted 3.5.24. Definite symptoms of diabetes had been present for ten months. Previous illnesses: rheumatism, bronchitis, and pleurisy a few years ago; a carbuncle two years previous to admission; pruritis and crops of boils six or seven months before she came under observation. Her personal and family history were unimportant; development and muscularity poor. The abdomen was well covered. Xanthochromic eruption on the face and hands. Discharged 12.6.24.

Throughout treatment the patient's weight remained about 14 per cent.

² The standards for height, weight, and age are taken from Joslin, *Treatment of Diabetes Mellitus*, 1924, p. 761.

above the average for her height and age. No gain or loss was observed during this period. The figures for her average daily diet showed no relation to the fasting blood values given in Table III, nor to the amount of insulin administered. It may also be noted that the xanthochromic eruption described in this case was not related to a high blood cholesterol.

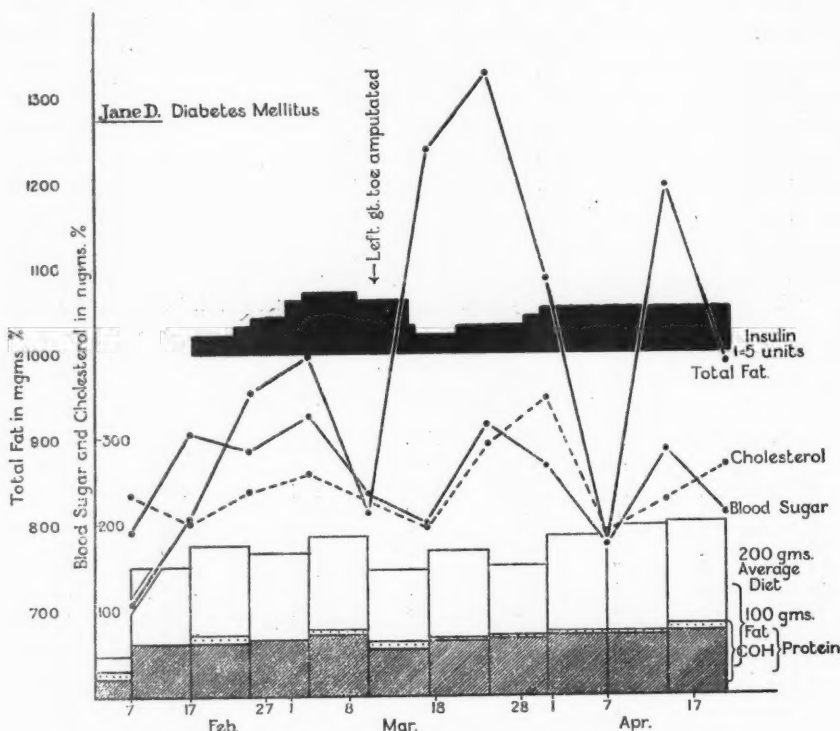


FIG. 1. Fasting blood chemistry and average daily diet of Case I.

TABLE III.

Fasting Blood Chemistry of Case II.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
5.5.24	244	763	193
12.5.24	200	1150	201
19.5.24	195	632	244
26.5.24	182	675	239
2.6.24	200	1019	245
9.6.24	200	801	255

Case III. Mrs. I. B., aged 64. Admitted 2.4.24. Thirst and polyuria for four months, also a considerable loss of weight, her greatest previous weight some years before having been thirteen stone, whereas now it was ten stone. Previous illness, nephritis in 1920. Personal and family history unimportant. On admission the urine contained 0.5 per cent. sugar and 0.14 per cent. albumin. She was treated without insulin and discharged on a diet of 2,100 calories per diem 20.4.24.

TABLE IV.

Fasting Blood Chemistry of Case III.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
4.4.24	364	1220	267
8.4.24	200	867	246
14.4.24	182	1177	226
21.4.24	121	1038	190

This patient's weight remained practically that of a standard normal person of the same height, sex, and age throughout treatment. No definite relationship could be established between the diet and the fasting blood chemistry (Table IV).

Case IV. J. W., aged 68. Admitted 23.1.23. Discharged 2.2.23. Re-admitted 14.2.24. On his second admission his complaint was pain and swelling, and ulceration and discoloration of the legs. The history of this condition went back some ten years. On examination, the left leg was found to be much more involved than the right, being oedematous and diffusely discoloured, with a discharging sinus on the dorsum of the foot. Sugar was found in the urine and the patient was put under dietetic treatment for diabetes. Discharged 23.3.24.

TABLE V.

Fasting Blood Chemistry of Case IV.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
18.2.24	121	503	158
25.2.24	133	713	182
3.3.24	141	755	175
10.3.24	95	811	221
17.3.24	102	1104	226

TABLE VI.

Average Daily Diet of Case IV.

Date.	COH. Grm.	Pr. Grm.	Fat. Grm.	G : FA.	Calories.
15.2.24-17.2.24	74	56	101	1.00	1421
18.2.24-24.2.24	44	47	105	1.42	1306
25.2.24- 2.3.24	60	56	145	1.47	1765
3.3.24- 9.3.24	63	58	15	1.47	1851
10.3.24-16.3.24	66	61	16 ¹	1.47	1959
17.3.24-22.3.24	72	65	17 ⁰	1.47	2143

While complicated by infection, there was no febrile disturbance. With the increase of fat in the diet the fasting blood-fats rose, the fatty acid portions being more affected than the cholesterol, although this rose from the lower to the upper middle reaches of normality as the patient's condition improved (Tables V and VI). The fatty acids, however, increased beyond the normal level very considerably, the extent of the rise being much greater than would have been seen even in the course of an ordinary alimentary lipaemia.

Case V. Mrs. H. W., aged 64. Admitted 6.5.24. She had suffered from diabetes for ten or twelve years. Previous illnesses: scarlet fever and rheumatic fever in childhood. Personal and family history unimportant. The urine on admission contained sugar and albumin. Discharged 2.6.24.

TABLE VII.

Fasting Blood Chemistry of Case V.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
12.5.24	137	908	186
19.5.24	124	828	239
26.5.24	143	643	185
2.6.24	181	1186	209

This patient was put on ten units of insulin per diem a week after admission and was rendered aglycosuric. The urine of 19.5.24 showed acetone in small amount, as it had also done for some three days previous. The G : FA ratio was kept low, never being higher than 1.37 on the average; the highest average daily fat in the diet was during the last fourteen days of her stay in hospital. Throughout her stay in hospital her weight was 3 to 4 per cent. above the normal. The findings in this case would seem to indicate that even acetonuria is not necessarily associated with a high blood-fat level (Table VII).

Case VI. Mrs. E. W., aged 54. Admitted 28.2.24. Diabetes for five years previous to admission. Discharged 28.3.24.

TABLE VIII.

Fasting Blood Chemistry of Case VI.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
3.3.24	382	862	196
10.3.24	—	1319	226
17.3.24	210	1319	208
24.3.24	357	1248	280

The patient was put on insulin five days after admission and made aglycosuric. Twenty units per diem were administered during the first four days, while subsequently the dose was increased to twenty-five units per diem. The fat in the diet was increasing throughout her stay in hospital. Her weight increased from 18 per cent. on admission to 15 per cent. on discharge. The total fat rose markedly, while the cholesterol, although it increased, remained within normal limits.

Case VII. Mrs. A. B., aged 58. Admitted 7.5.24. Diabetes complicated with pulmonary tuberculosis, the duration of both conditions being uncertain. There had been an exacerbation of the diabetes during the six months before admission. There was also an infection of the genito-urinary tract by *Bacillus coli*. The patient had sugar in the urine on admission. Transferred to a sanatorium for treatment of her tuberculosis after having been put under suitable dietetic treatment, 13.6.24.

TABLE IX.

Fasting Blood Chemistry of Case VII.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
12.5.24	200	963	210
19.5.24	235	694	208
26.5.24	193	790	188
2.6.24	235	1084	185
9.6.24	215	690	233

The diabetes in this case was probably very chronic. The temperature during her stay in hospital often showed an irregular evening rise to about 100° F. On admission her weight was 37 per cent. below the standard, and on discharge 40 per cent. below. She was started on insulin nine days after admission, with, at first, 10 units per diem; later, 15 units per diem. No relation could be found between dietary fat and the fasting blood-fats as shown in Table IX.

Case VIII. T. G., aged 49. Admitted 21.2.24. Diabetes for two years with marked loss of weight. Personal and family history unimportant.

TABLE X.

Fasting Blood Chemistry of Case VIII.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
25.2.24	202	1036	256
3.3.24	246	750	255
10.3.24	95	983	230
17.3.24	222	1148	234
24.3.24	253	1175	253

The patient's weight on admission was 10 per cent. below the normal and on his discharge, on the 25.3.24, 12 per cent. below the normal. During the first ten days of his stay in hospital there was a rapid decrease in the total fats of the fasting blood when the average G:FA ratio was unity or even lower, thus allowing for a possible burning up of excess fat. The decrease involved only the fatty acids, the cholesterol remaining steady. Later, the blood-fats rose again as the fat in the diet increased, even although insulin was being administered during the last fortnight of his stay in hospital (Table X).

Case IX. Mrs. B. S., aged 46. Admitted 15.2.24. Diabetes of uncertain duration, but becoming more intense during the twelve months previous to admission. The urine contained sugar on admission, but no acetone.

TABLE XI.

Fasting Blood Chemistry of Case IX.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
18.2.24	267	559	186
25.2.24	99	754	220
3.3.24	124	821	196
10.3.24	194	878	270
17.3.24	129	1278	233
24.3.24	270	1346	262

Insulin was administered almost immediately after admission in this case, the average daily dose during the last month of her stay in hospital being 30 units. Notwithstanding, the total blood-fat rose steadily under treatment, the cholesterol showing also a similar but less marked increase (Table XI). The G:FA ratio throughout was never above 1.6, and the patient gained in weight from 31 per cent. below the standard on admission to 18 per cent. below the standard on discharge, 27.3.24.

Case X. W. S., aged 41. Admitted 18.3.24. The diabetes in this case was of uncertain duration, having been discovered three months before admission by an ophthalmologist to whom he had gone because of failure of the sight of the right eye, which had been becoming worse during the previous twelve months.

His weight was 23 per cent. below standard on admission, and on his discharge 26.4.24, it was 24 per cent. below.

Readmitted 11.5.24 after dietary indiscretion. His diet had to be built up again, an undertaking which was as difficult as it had been during his previous stay in hospital. Discharged 6.6.24.

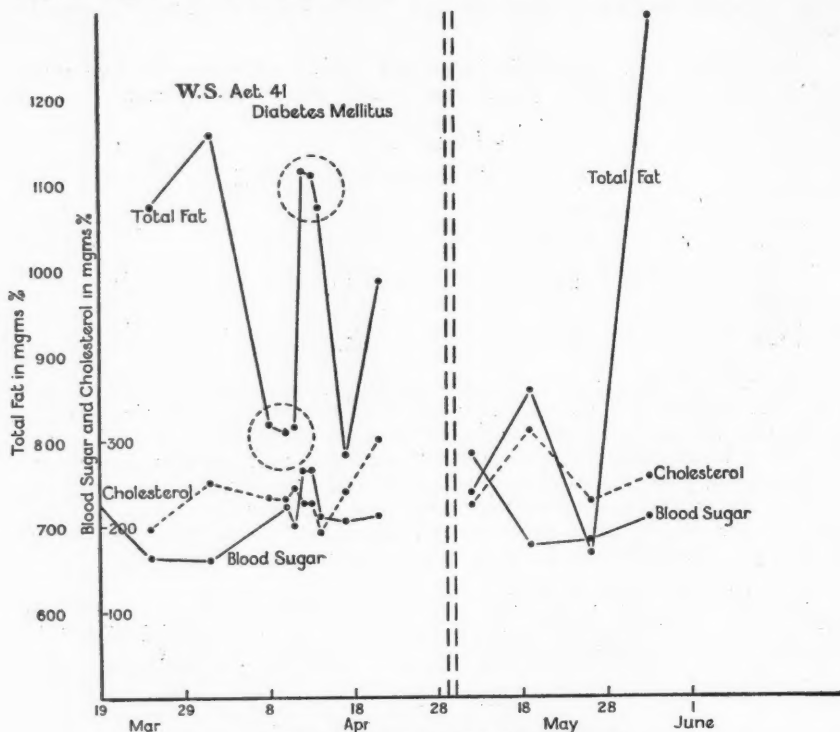


FIG. 2. Fasting blood chemistry of Case X.
The circles indicate the figures referred to in the text.

TABLE XII.

Fasting Blood Chemistry of Case X.

Date.	Blood-sugar. Mg. %.	Total Fat, Mg. %.	Cholesterol. Mg. %.
18.3.24	233	—	—
24.3.24	161	1075	197
1.4.24	160	1158	250
8.4.24	—	816	231
10.4.24	222	809	230
11.4.24	200	813	244
12.4.24	265	1114	226
13.4.24	265	1110	226
14.4.24	210	1072	191
17.4.24	205	763	241
21.4.24	210	987	300
11.5.24	Readmitted		
12.5.24	285	739	224
19.5.24	177	858	310
26.5.24	182	668	220
2.6.24	210	1296	256

During the period 11.4.24-17.4.24 the patient received 100 grm. per diem of the synthetic odd-carbon fat, intarvin. At no time, however, did the G:FA ratio rise above 1.5. With the rise of fat in the diet during his first stay in hospital there was no constant change in the total fat figures. During his second stay with the increase of fat in the diet, and about 30-40 units of insulin a day, the total fat finally attained its highest figure (Table XII and Fig. 2). This case was complicated by the presence of sepsis, and after the extraction of the septic teeth, 28.5.24, acetone was found in the urine for six days.

Case XI. Mrs. W., aged 35. Admitted 19.11.23. Diabetes of uncertain duration, becoming progressively worse in the previous three months. This was accompanied by a marked loss in weight.

TABLE XIII.

Fasting Blood Chemistry of Case XI.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
21.1.24	138	526	236
23.1.24	125	746	235
4.2.24	159	539	275
11.2.24	206	573	227
17.2.24	143	749	192
25.2.24	136	830	231

The observations in this case were started some time after the beginning of treatment. The insulin dosage was being reduced and the fats in the diet were increasing, while the G:FA ratio remained 1.5. On admission the patient's weight was 20 per cent. below standard, and on discharge, 27.2.24, 18 per cent. below. The blood-fat showed an irregular rise (Table XIII), but the blood cholesterol was relatively steadier.

Case XII. Mrs. A., aged 30. Admitted 22.1.24. Diabetes becoming more intense in the course of the previous seven months. She had lost 2 st. in weight since the commencement of the disease. Previous illnesses and family history unimportant.

TABLE XIV.

Fasting Blood Chemistry of Case XII.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
23.1.24	194	819	234
4.2.24	190	699	258
11.2.24	143	798	276
18.2.24	201	780	219
25.2.24	191	887	293
3.3.24	290	881	268
10.3.24	250	929	261
17.3.24	250	1436	231
24.3.24	324	1207	236

The patient gained weight during her stay in hospital from 11 per cent. to 1 per cent. below the standard on her discharge, 27.3.24. As can be seen from Fig. 3, no obvious relationship could be established between food-fat, blood-fat, or insulin administered.

TABLE XV.
Average Daily Diet of Case XII.

Date.	COH. Grm.	Pr. Grm.	Fat. Grm.	G: FA.	Calories.	Insulin Units.
22.1.24-27.1.24	42	35	54	0.96	791	—
28.1.24- 3.2.24	30	30	49	1.11	678	—
4.2.24-10.2.24	39	38	70	1.20	950	—
11.2.24-17.2.24	62	61	157	1.49	1902	—
18.2.24-24.2.24	55	54	136	1.47	1940	7
25.2.24- 2.3.24	89	75	216	1.49	2595	14
3.3.24- 9.3.24	86	77	212	1.49	2567	23
10.3.24-16.3.24	71	66	180	1.51	2164	23
17.3.24-23.3.24	63	61	161	1.52	1947	18
24.3.24-27.3.24	58	57	143	1.48	1746	23

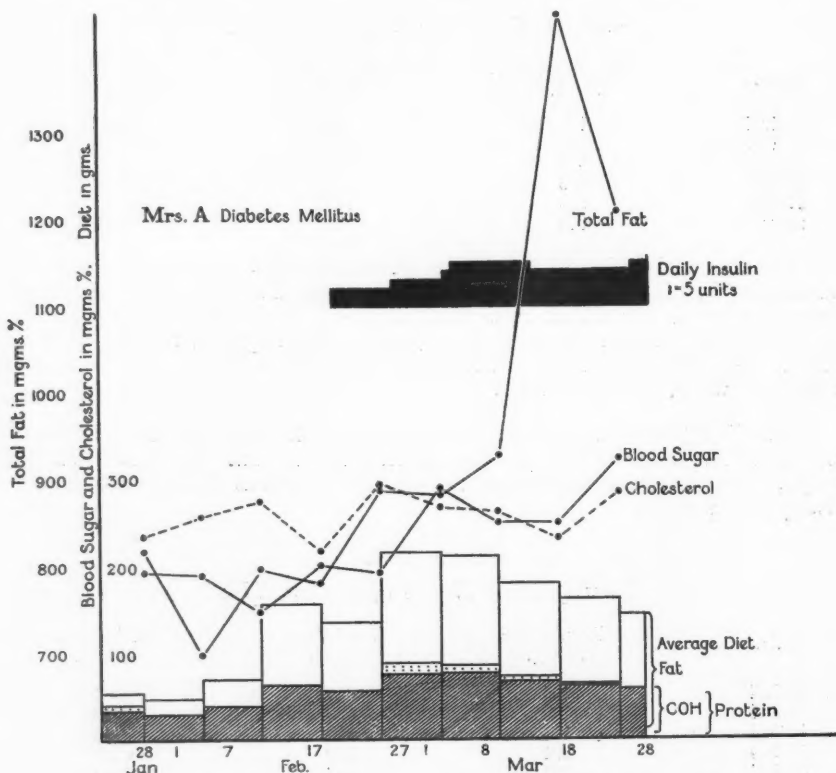


FIG. 3. Fasting blood chemistry and average daily diet of Case XII.

Case XIII. Esther L., aged 30. Admitted 1.4.24. Diabetes for five months with loss of weight. The breath on admission was loaded with acetone. Previous illnesses unimportant.

This case was a severe one, contrasted with the others, on admission. She was in a condition of acidosis. Under intensive insulin treatment the total fats fell, the decrease being in large part due to the great lowering of the cholesterol figures. The blood-sugar, too, came much nearer a normal level as a result of treatment. Table XVII gives the average daily diet of the patient during

hospital treatment, allowance being made for the extensive loss of sugar that took place during the first week of treatment in the calculation of the caloric value and G : FA ratio of the diet.

TABLE XVI.
Fasting Blood Chemistry of Case XIII.

Date.	Blood-sugar. Mg. %.	Total Fat. Mg. %.	Cholesterol. Mg. %.
4.4.24	300	1316	511
14.4.24	222	1406	306
21.4.24	105	1109	273
28.4.24	154	1165	217

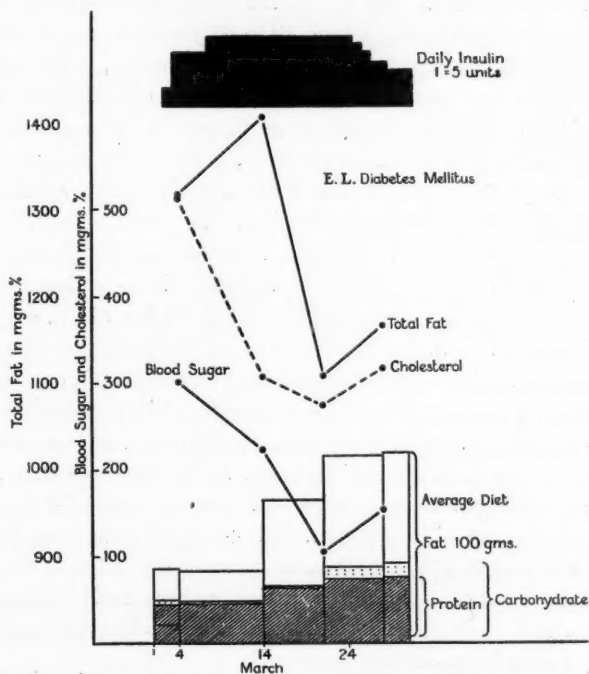


FIG. 4. Fasting blood chemistry and average daily diet of Case XIII.

TABLE XVII.
Average Daily Diet of Case XIII.

Date.	COH. Grm.	Pr. Grm.	Fat. Grm.	G : FA.	Calories.	Insulin Units.
1.4.24- 3.4.24	22	50	85	1.67	1047	3
4.4.24-13.4.24	49	45	82	1.04	1113	33
14.4.24-20.4.24	64	62	163	1.48	1975	40
21.4.24-27.4.24	88	74	214	1.50	2574	36
28.4.24- 1.5.24	91	75	218	1.50	2617	21

The patient's weight rose from -40 per cent. on admission to -35 per cent. on discharge, 1.5.24. In Fig. 4 are represented the findings given in Tables XVI and XVII.

Discussion.

While the data are insufficient to allow of any broad generalization being drawn, there are sufficient facts to allow certain tentative conclusions to be brought forward. The cases may be discussed under several headings—the age and nutritional condition of the patient during treatment, the relation of diet and the value of the G:FA ratio, the relation of insulin, and the relation of the type of reaction shown by the patient to prognosis.

Age and nutritional condition of the patient. From the figures available it would seem that the age of the patient had no influence on the type of response shown by the blood-lipids. The ages of the nine patients showing a rise in the blood-fats under treatment ranged from 30 to 68 years, the ages of the two cases showing a definite fall were 30 and 64 years respectively, while the remaining two, who showed a more irregular type of response, were 58 and 61 years old. Although these data are in themselves insufficient to allow one to state categorically that no relationship exists between the age of the patient and the type of response, the probability that this is the case is further confirmed by the series of cases reported by Blau and Nicholson (23), where, in a study of 26 cases, no such relationship was found. It has been shown that, in diabetes, a subnormal body-weight tends to be associated with a higher blood-fat than a body-weight above the standard for the given height and age (7, *loc. cit.*, p. 100). In those cases that showed a rise in the blood-fats under treatment the average weights on admission varied from -40 per cent. to +7 per cent. and on discharge from -35 per cent. to +7 per cent.; where there was a fall, the weights were in the two cases, -40 per cent. and +2 per cent. on admission, and on discharge -35 per cent. and -1 per cent. respectively; and in the two cases with an irregular response, the weights on admission were -37 per cent. and +14 per cent., while on discharge they were -40 per cent. and +14 per cent. respectively. Consequently, if the weight of the patient be taken as an index of the nutritional condition of the patient, the weight of the patient, either on admission or discharge, has little to do with the type of response that may be observed under treatment, at least as far as the blood-fats are concerned.

The relation of diet and the value of the G:FA ratio. Turning now to the influence of diet in the cases, several factors must be taken into account. The tables given under Cases I, IV, XII, and XIII show no relation between the amount of fat in the diet and the fasting blood-fat level. The average daily diets of the other cases showed this lack of relationship as distinctly as those cited in the tables. It will be noted, especially in Figs. 1 and 2, that the blood-fats are subject to marked individual variations, the cause of which is not obvious. That these are not due to errors in the method of estimation may be concluded from the figures given under Case X and diagrammatically in Fig. 2, where three readings, those for the 8th, 10th, and 11th of April, remained constant at about 800 mg. per cent. total fat, and were immediately followed by three readings, those of the 12th, 13th, and 14th of the same month, varying between

1,000 and 1,100 mg. per cent., to be followed in three days' time by another reading much nearer the early 800 mg. per cent. Whether these are simply exaggerations of the normal variations or peculiar to the condition cannot be stated. Certainly, a more accurate and if possible non-nephelometric method of determining the blood-fat would be of great value in establishing the significance of these findings, in virtue of the greater precision that would be attained. The diets in the cases under consideration were all constructed on the same principles, due regard being paid to the ketogenic-antiketogenic balance as set forth by Woodyatt and Shaffer and their co-workers. At no time was the G:FA ratio above 1.6, thus allowing ample control of possible ketone production. Despite the sufficiency of the ratio the blood-fats show no definite relation to the amount of fat in the diet either directly or indirectly. At this point it would be useful to consider the question of β -oxidation of the fatty acids in relation to the problem of diabetes, a subject of great interest in view of the recent attempts to avoid ketosis by administering a synthetic odd-carbon fat instead of the usual even-carbon fats of the diet. If the β -oxidation theory held completely, the odd-carbon fat, containing as it does an uneven number of carbon atoms, could not be finally oxidized to aceto-acetic acid and then to carbon dioxide and water, but would pass through the stage of propionic acid and thus avoid the possibility of ketosis and its associated dangers. The results which have been published with regard to its use have not been uniform. Kahn, in three papers (24), reported very favourably on this fat (intarvin), as also did Desgrez, Bierry, and Rathery (25), Joslin (26), and F. S. Modern (27), while Keefer, Perlzweig, and McCann (28) report that it is probable, but not certain, that intarvin gives rise to less ketosis than an equivalent amount of fat in the diet. Lyon, Robson, and White (29) came to a similar conclusion, that, while it did not prevent ketone formation, the amount formed was less than when an equivalent amount of fat was added to the diet. At the other extreme we have the statement of Sevringhaus (30) that it seemed to have little or no ketolytic value apart from its glycerol content, and that it did not exert a protein-sparing action in the diets he used. It would seem, then, that β -oxidation did not wholly explain the catabolism of the fatty acids, or else the intarvin, although adequately absorbed, was not used completely by the organism, but was stored, and some of the normal fat of the body was used instead. There is, however, some evidence that the β -oxidation mechanism is not the sole mechanism connected with metabolism of fat. For instance, Leathes and Meyer Wedell (31) showed that, after the ingestion of fat, the fat found in the liver might attain a much higher iodine value than that of the food administered. Dakin (32) gives two possible explanations of this: either new double linkages are introduced into the fatty acid molecule by oxidation, a view which was put forward in the original paper, or structurally isomeric unsaturated acids which absorb iodine more readily are formed by intramolecular rearrangement. The experiments of Hartley (33) on the fatty acids isolated from the liver of the pig throw some light on this question. He showed that the oleic acid of the pig liver differed from the oleic acid of the pig connective

tissue in the position of the double bond. He was also able to demonstrate the presence of tetrahydroxystearic acid in the pig liver. Similarly, Raper (34) found that after feeding coco-nut oil the volatile fatty acids isolated from the liver had higher iodine values than those of the original oil. The exact significance of this desaturation is not known. *In vitro* the unsaturated fatty acids readily break down at the unsaturated linkage, but there is no clear evidence that such takes place *in vivo*. Nevertheless it would appear likely that the fatty acids are more prone to attack at the unsaturated linkage. If such a disruption takes place, then there is, as Leathes and Raper (35) point out, the possibility of fatty acids being formed containing an uneven number of carbon atoms like those which Ringer (36) showed did not increase the formation but rather led to an increase in the formation of glucose. Acting on this hypothesis, Mottram failed to lessen the excretion of acetone in diabetic patients when the highly unsaturated cod-liver oil was substituted for the butter of the diet (37) in experiments of short duration. It would appear possible that the partial success of intarvin has been due to some such cause, since if the intarvin molecule were desaturated by the liver and rupture took place at the unsaturated linkage, then there would be formed at least one fatty acid containing an even number of carbon atoms which could give rise to ketone bodies. Recently, too, Clutterbuck and Raper (38), using hydrogen peroxide, the reagent which gave strongest support from the chemical standpoint to the theory of β -oxidation, have shown that the ammonium salts of the higher fatty acids may undergo not only β -oxidation but γ -oxidation and δ -oxidation, mechanisms which if found *in vivo* may explain how fat is enabled to supply energy for the contraction processes of muscle, which is predominantly a carbohydrate machine. Thus, while β -oxidation plays an important part in metabolism, it cannot explain all the possibilities that may occur in any one case. Further, Palmer and Ladd (39) have shown that fat may be given in certain cases of diabetes with much higher G:FA ratios than are usually given, and that as treatment is continued such cases may excrete proportionately less acetone even although they are being kept on the same high fat diet. The work of Dubois and Richardson shows that it is inaccurate to compute the carbohydrate and fat burned from the carbohydrate and fat ingested, the only method of computation with a reasonable claim to accuracy being calorimetric determination. Secondly, the assumptions upon which the G:FA ratios are based are in all probability too rigid. The factors used are all maximal factors, and as such may be liable to considerable individual variation, exerting their maximum ketogenic or antiketogenic power at one time and less than this at another, according as metabolism demands it. These ratios, then, may be liable to considerable error and can only be taken as approximations to the truth. Consequently, any relation between the fat of the food and the fasting blood-fat level cannot be very distinct. Certainly it has been shown that in the normal organism prolonged fat feeding tends to raise the blood-fat level, yet, in the cases reported in this series, where there was generally a gradual rise in the fat of the diet to supply sufficient calories for the patient's activities, the blood-fat did not necessarily rise along with it; in many

cases the increased blood-fat occurred when the dietary fat was being lowered. Similarly, Marsh and Waller (40) have shown that feeding diabetes on a diet containing fat in greater proportion than is customary under the other systems of treatment may only keep the blood-fat steady at a higher level than normal. As a result of the patient's lowered tolerance for carbohydrate there is a relative increase in the diet of those substances which tend to make the blood-fats more unstable, namely, protein and fat. How far these factors may be working in any given case cannot be stated with any accuracy, but the importance of the lowering of the carbohydrate ration in the causation of hyperlipidaemia has been noted by Joslin, Bloor, and Gray (41), just as, conversely, the presence of an excess of fat in the diet may lower the glucose tolerance (Greenwald, Gross, and Samet (42)). The long duration of the effect of protein shown by Sakai (10) must always be kept in mind when considering the blood-lipoid level. It would seem that the usual twelve hours' fast might not be sufficient to get the blood-fat to an absolutely basal level. The fourteen hours' fast of Joslin is probably nearer the true fasting level. In cases where there are very high blood-fats, conditions are rather different; there, fasting itself will tend to lower the values. The effect of fasting on the blood lipoids in the normal animal seems to vary with the state of nutrition of the animal. Therefore it would seem desirable, when studying the blood-fats, to control these factors as closely as possible by having the patient under a constant régime for several days before taking the blood for examination, the patient fasting for fourteen hours at least before the taking of the specimen.

Insulin and the blood-fat. There seems to be little doubt that insulin brings about a lowering of the blood-fats when these have reached a high level, such as may occur in severe cases of diabetes. Several instances of this are to be found in the clinical literature on the subject. In a case which showed considerable acidosis, with a marked lipaemia visible to the naked eye, the administration of insulin greatly lessened the acidosis, and the lipaemia as determined by the naked eye was also greatly diminished within three hours (Davies *et alii* (43)). Mcleod (44) gives figures for the action of insulin on the fat-content of the liver and blood in experimental diabetes where a marked fall in the fat-content of both occurred with remarkable rapidity. These results are of interest when considered along with the prompt effect of insulin on the excretion of the ketone bodies. The action on the ketone bodies, however, cannot be described as direct, since Hirschfelder and Maxwell (45), confirming the observations of Robertson and Anderson (46), have shown that insulin has no effect in reducing the toxicity of the acetone bodies when these are administered to experimental animals. The action of insulin on the blood-fat in such conditions would therefore appear to be indirect and due to the improved carbohydrate metabolism that follows its injection. This conclusion is further confirmed by the experiments of Hartmann (47), who found that the changes in the blood-fats after a meal containing fat and oatmeal were similar, whether insulin was given or not. Nevertheless it has been found that associated with the extreme effects of insulin on the blood-sugar there may be a migration of fat from the liver to the muscles (Raper and Smith

(48)). These changes only occurred when hypoglycaemia was produced and were associated with increased blood-fats, and therefore are not inconsistent with the findings of Hartmann. The possibility of insulin causing the conversion of carbohydrate into fat is still too problematic to be considered in connexion with the changes in the blood-fat, and will not be considered here. There are relatively few figures relating to the effect of the prolonged administration of insulin on the blood-fats. But Joslin (49) gives two sets of figures for cases of his own, where there was a definite fall, although the last reading in the second case he quotes after nine months' treatment with insulin was higher than the previous reading taken six months before, showing a 50 per cent. increase, being 1.00 grm. per cent. as compared with the previous 0.67 grm. per cent. Gray and Root (50) give figures for a case of lipaemia retinalis where the blood-fat under insulin fell from 6.3 to 2.2 per cent. within six days. Rowe (51) records an extreme case of diabetic lipaemia with lipaemia retinalis where, after two months' treatment with insulin and a low fat diet, the blood-fat fell from approximately 15 per cent. to 1.25 per cent. In this case all the factors would seem to have been favourable to the rapid control of the excess of the blood-fat, but nevertheless the lipaemia was not exceptionally rapid in clearing up, although the carbohydrate metabolism as reflected by the blood-sugar was rapidly brought under control. Thus even with a very low G:FA ratio, such as was given in this case, one which was on the average nearer 0.7 than 0.8 throughout the period of treatment, the excess of fat may take some considerable time to disappear. The addition of insulin to the treatment of a case will certainly improve the carbohydrate metabolism, and indirectly, at any rate, facilitate the metabolism of fat. Further than this it is unwise to go at present.

Blood-fat and prognosis. The importance of the blood-fat in relation to prognosis has been urged for some time, some holding that it is more important than the estimation of the blood-sugar as an index of prognosis. Blau and Nicholson (23) divided their cases into four groups according to the type of reaction shown by the blood-fats: (1) a group in which the blood-fat increased steadily or intermittently, while the blood-sugar fell, associated with a bad prognosis; (2) a group in which the blood-fat more or less paralleled the blood-sugar and where the prognosis was not so unfavourable; (3) a group in which the blood-fat stayed practically at the same level and in which infection seemed to be an aetiological or at least a predisposing factor; and (4) a number of cases which could not be placed in any of these groups. The cases considered are too few to form the basis of statistical investigation. The majority of them would seem to belong to the second group according to the above classification where the prognosis is not so unfavourable. Cases II and V seem to belong to the unclassified group, while Cases IV, VI, and IX would seem to belong to Group I. The history of these cases since their discharge has been that on the average they have all remained in equilibrium up to the present time. Gray (52), from an examination of 1,000 diabetic bloods, also found that the course of the blood-fats under treatment was much more difficult of interpretation than the blood-sugar,

and that the blood-fat varied considerably in the individual case, while on the average it seemed to be fairly parallel to the blood-sugar. It would therefore appear probable that if the blood-fat or cholesterol are to be used as prognostic agents further data are desirable.

Summary.

1. Data are given as to the reaction of the blood-fats in 13 cases of diabetes mellitus under treatment, all of which, except two, were treated during some part of their stay in hospital with insulin.

2. The possible factors influencing the blood-fat level are considered and the difficulty of obtaining any definite correlation between them noted.

3. The necessity for further observation, if blood-fats are to be used for prognosis, is emphasized.

In concluding, the writer desires to express his thanks to Professor Murray Lyon for his criticism and advice.

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OBSERVATIONS ON THE DEVELOPMENT OF CONTRA-LATERAL DISEASE IN ARTIFICIAL PNEUMOTHORAX THERAPY¹

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With Plates 18-24

Introduction.

OUT of one series of thirty artificial pneumothorax cases, which have been under observation during the past three years, and from which have been selected the six examples quoted, twenty-two have been cases of pulmonary tuberculosis and four cases of bronchiectasis. The remaining four were patients in whom the diagnosis was uncertain and in whom artificial pneumothorax was used in conjunction with radiology as an aid to diagnosis, apart altogether from the question of treatment. Except in the last mentioned, the technique as regards pressures, spacing of refills, &c., has been conducted in the main on similar lines to those of most other observers, and comparison of the general results over the period in question, so far as concerns the progress of phthisical patients, has not led to any widely different view as to the present value and limitations of artificial pneumothorax therapy. One impression in particular has, however, been gained. It would appear that the details of the management of a case, especially in regard to the pressures maintained, are of much greater importance and difficulty than is generally appreciated, and that a good deal has yet to be learned in respect of procedure, particularly in the later stages of treatment. Certain apparent discrepancies in results led to the selection of these particular cases for special study, since they seemed to illustrate features of importance relating to the development of disease in the untreated lung. The first three were patients in whom the disease appeared to be practically unilateral, the opposite lung having at any rate shown no definite signs of active disease, and being both clinically and radiologically sound; the prospects of success were good and the development of contralateral disease was not anticipated, nevertheless, by reason of its appearance at a later date, the pneumothorax had to be stopped. Conversely, in the last three patients treatment was begun with considerable misgiving owing to the condition of the opposite lung, yet the results were successful beyond expectation, and to an extent at least which

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justified the decision to attempt a pneumothorax. It was felt that a closer comparison of these cases might be of value, and might explain some of the discrepancies in results and possibly lead to a better understanding of the causes of failure and of the conditions under which the relatively sound lung becomes the seat of active disease after a period of complete quiescence. Attention has been drawn to details in regard to intrapleural pressures, and an endeavour made to correlate these with certain clinical and radiological features in the hope of being able to elucidate further facts in regard to the development of contralateral disease which may have some bearing not only upon the initial choice of cases for artificial pneumothorax, but also upon the actual details of the technique. One of the most important points in the management of such patients is the provision of adequate X-ray control and the careful study of the skiagrams taken from time to time. It has been impossible for reasons of economy of space to reproduce all the radiograms taken of these cases, but those given here have been selected in order to call attention to the salient features under consideration. It must be remembered that no prints or transparencies, however carefully prepared, can ever give the precise information afforded by study of the original negative.

The induction of a pneumothorax on one side in cases where the opposite lung is involved is open to the obvious objection that collapse of the worse lung, which is thereby put out of action to an extent varying with the degree of collapse obtained, throws a considerable amount of extra strain upon the sounder lung, with a corresponding risk of stirring up any focus of disease present therein and increasing its activity by contradicting the very principle of rest which it is our object to maintain. It is, however, recognized that when inflammatory conditions are present in the body involving a considerable area of tissue, elimination or arrest of disease at the site of maximum infection may, and often does, result in the clearing up of pathological processes in areas which are more remote. This is a statement in terms of general pathology which can be properly applied to the question of artificial pneumothorax in tuberculosis. Many patients are to-day treated with a reasonable amount of success who formerly would have been excluded as entirely unsuitable. Too much stress has perhaps been laid upon the anatomical extent of disease in the relatively good lung, a more important question being the degree of activity of such disease, so far as we are able to estimate this. It is likely that a patient in whom there is evidence of a fairly considerable extent of morbid change in the better lung will, provided this be quiescent, react much more favourably to treatment than will one in whom the sounder lung is affected by disease less in extent but yet active. In other words, the main contra-indication to artificial pneumothorax, so far as concerns the condition of the untreated lung, is probably not so much contralateral disease as contralateral activity.

The Determination of the Degree of Activity of Disease.

This in the relatively sound lung is a matter upon which we possess no absolutely reliable clinical data. During the preliminary period of observation of a patient for whom artificial pneumothorax is contemplated, attention is directed to the physical signs, and especially to the presence or absence of moist sounds in the good lung, and, if moist sounds are present, to their persistence and variability. It is a matter of experience that, after induction of a pneumothorax on the side which shows evidence of gross disease, signs of activity in the opposite lung often clear up after a certain degree of collapse has been obtained. It would appear that this is due partly to the reduction of toxæmia resulting from successful collapse of the bad lung and corresponding with the drop in temperature and general improvement in the patient's condition, and partly to the beneficial effects of moderate compression of the other lung produced by displacement of the heart and mediastinum. The degree of compression of the opposite lung and its effect upon any focus of disease therein is one of the most important points affecting the whole question of technique.

Simon (1) gives some interesting and valuable observations in a clinical and radiological study of cases of pulmonary tuberculosis with special reference to the effects of artificial pneumothorax on the untreated lung. From the study of pressures in the pleural cavity, both in the human subject and in goats, it appears that the manometric readings on the collateral side are closely parallel to those on the treated side both before and after the production of an artificial pneumothorax. He quotes Schill (2), who divides the opinions of various observers on this point into three groups. In the first are included those who believe that the pneumothorax exerts a harmful effect on the opposite lung; the actual cases quoted, however, only represent 12 to 15 per cent. of cases treated. In the second are included those who believe that the effect on the opposite lung is a beneficial one, and here again the cases reported are not numerous. The third group comprises those who believe that there is very little, if any, effect upon the opposite side; this, according to Schill, is by far the most prevalent opinion. Simon (*loc. cit.*) considers it extremely difficult to determine the percentage of cases in which the uncollapsed lung is detrimentally affected by artificial pneumothorax treatment, but concludes that while it varies with individual experience the general consensus of opinion is that in most cases benefit results.

Most important in this connexion is the condition of the mediastinum. Stivelman, Hennell, and Golembe (3) regard the thorax, from the standpoint of pressure relations, as one cavity rather than two, any change in the pressure in one pleural cavity being found to affect the other one almost equally. They quote Simon (*loc. cit.*) and also Graham and Bell (17) and Betchov (18), and corroborate the results of these observers in their own experiments on dogs. They say, 'In the presence of a flexible mediastinum the intrathoracic equilibrium in pneumothorax is very delicately adjusted, and any disturbance in the intrathoracic pressure on the treated side will have a proportionate effect on the

intrathoracic pressure on the untreated side, as well as produce a readjustment in the position of the mediastinal structures. On the other hand, with a mediastinum effectively fixed by adhesions, the effect of unilateral pneumothorax on the opposite side is practically negligible, for the rigid mediastinum will stand the brunt of the increasing intrathoracic pressure on the pneumothorax side without transmitting it to the untreated side.' They consider that this principle affects the procedure in different cases: e.g. when the mediastinum is fixed, or the pneumothorax limited by adhesions, or both, very high pressures will cause no appreciable effects on the untreated lung; if the pneumothorax cavity is closing up, they think it justifiable to prevent this by raising the pressures and keeping the pneumothorax in being. If on the other hand the mediastinum is not fixed by adhesions, increased pressure on the pneumothorax side will mean not only proportionate increase of pressure on the opposite side, but also a definite compression of the untreated lung. They urge that, with one lung collapsed and the untreated lung somewhat involved, every effort should be made to embarrass as little as possible the untreated organ which is being forced to carry on the work of respiration almost unaided, and they suggest that many of the failures in pneumothorax therapy are doubtless due to the reactivating of tuberculous foci in the untreated lung, and might have been avoided by a more thorough appreciation of the pneumo-dynamics involved. In the conclusion of their paper they observe that moderate compression of the untreated side may be beneficial in that it arrests the progress of disease in tuberculous foci in this lung, but if the compression be too great it embarrasses the action of the lung and causes increased inspiratory efforts, and this, from the 'crowding' and greater amount of atelectasis, adds to the disability and increases the activity of the disease.

No deductions are reached by these authors which serve as an accurate guide to pressure criteria, i.e. to the limits within which, in a given case, compression of the untreated lung is safe, and beyond which it is harmful. My experience on the whole has been that in case of doubt it is better to err on the side of too little compression.

Selective Collapse.

Considerable attention has been paid in the last few years to this principle in artificial pneumothorax, and reference must be made to this as having some bearing on the present investigation. As long ago as 1913 Parry Morgan (4) pointed out the possibilities of achieving by partial pneumothorax the advantages of a complete pneumothorax, and demonstrated that when there is a tuberculous focus in a lung there is during inspiration an increase in the elastic tension along any axis which passes through the focus of consolidation; he further showed that when air has been introduced into the pleural cavity separating the two pleural membranes the gas displaced during inspiration tends to accumulate over the less expansile portions of the lung and so to prevent the increase in

tension which would occur if the gas were not there. In a later communication (5) he observes that partial collapse of a tuberculous lung tends to give rest to any consolidated portion and thereby to reduce auto-inoculation. This principle has been worked out in some detail by many of the American observers. Barlow (6), discussing the behaviour of diseased portions of the lung where a partial pneumothorax exists, shows that, if the lesion is not too severe, inflammation or irritation of the tissue in any region of the lung causes a tendency of the involved tissue to collapse; after introduction of gas into a pleural cavity free from adhesions this principle of selective collapse is unhindered, the lung having no longer to conform in shape to the thoracic cavity, and the gas collects over the most involved regions. The importance of this in the practical application of pneumothorax therapy is further emphasized in another paper by the same author (7), in which he maintains that in cases of selective collapse following a partial pneumothorax the respiratory movements are taken up by the unaffected portions of the lung, and he urges the adoption of partial pneumothorax in preference to complete collapse on the grounds that there is little or no displacement of viscera, little interference with either circulation or respiration, and no imposition of extra function upon the opposite lung, which is frequently diseased. The same plea for the introduction of smaller amounts of air is advanced by Barlow and Kramer (8), who, while admitting certain disadvantages of this method, the least of which is that it requires considerably more skill in management, insist at the same time on the following advantages, viz. the avoidance of extra function of the opposite lung, the comparative avoidance of visceral displacement, and the lack of interference with the circulation. They consider that the cases suitable for complete collapse form but a very small proportion (1 to 5 per cent.) of all those with which they have to deal, and they find that not only have they obtained equally good results with much less disturbance to the patient, but that in cases where the amount of disease in the better lung has precluded complete pneumothorax they have not had a single instance in two years in which the disease on the untreated side was made worse. The whole question is one of the utmost importance, and while the evidence, both theoretical and practical, in favour of the employment of partial as against complete collapse is convincing, there is still a good deal to be said on the other side, especially in regard to many cases in which the disease, though unilateral, is producing a considerable amount of constitutional disturbance.

Selection of Cases.

Of the six cases quoted in this paper it may be observed that in the first three the history in regard to the onset of manifest tuberculosis was short, and the disease of more acute type, especially in Nos. II and III, than in the last three, in which the history was longer and the disease slower in its development. The tendency of acute cases to run a less favourable course has been commented on by most observers. Schill (2), in his concluding remarks on the effects of pneumo-

thorax pressure upon the opposite lung, notes that in those cases which were definitely reported as being harmed on the collateral side the period of observation was very short, and the cases were of the acute pneumonic and malignant types, considered unsuitable for any treatment, and therefore worthless as criteria for artificial pneumothorax. The Matsons (9), quoting from a very large number of cases, find that spread of activity in the untreated lung is more frequent in the acute types of diseases (*vide infra*). Burrell (10), in the report issued to the Medical Research Council, notes that acute cases do badly as a rule, and takes this into consideration among the factors which should influence one's initial choice. That this is true when applied to the more extensive methods of collapse involved in thoracoplasty there can be no doubt, and few surgeons are willing to operate on very acute cases, partly on account of the greater operative risks under these circumstances, partly owing to the finality of the collapse which, once achieved by a thoracoplasty, cannot be undone. In artificial pneumothorax, however, in which the results are not so irrevocable, the cause for hesitation is less, and since the more acute cases are the ones in which the urgency of the need for collapse is all the more apparent, one is inclined for this reason to take a greater amount of risk as regards the behaviour of the collateral lung than in the chronic types in which the urgency is considerably less. The question of length of treatment should be regarded as a much more important matter in acute than in chronic disease, collapse in the latter being a safer procedure, even when continued indefinitely, whereas in the more rapidly progressing type of tuberculosis more discrimination may be required as to the length of time for which treatment should be continued, and greater watchfulness as to any indications for relaxing the pressure.

A further point which calls for comment is the fact that in Cases I to III the pneumothorax was on the right side, in Cases IV to VI it was on the left side. It may be mentioned that in the selection of these particular patients for quotation no special account was taken of this fact, which was only noted subsequently, but which raises an important matter for discussion. Although there has been a certain amount of speculation as to the relation of the side treated (right or left) to prognosis, there has been surprisingly little tabulation of figures. Those given by Bull (11), although relating entirely to extrapleural thoracoplasty, and the operative mortality thereof, may possibly have some bearing on treatment by artificial pneumothorax. Of 92 operations performed over a period from May 1, 1914, to Nov. 1, 1923, 56 were on the left side, the operative mortality (i.e. death from 1 to 23 days, average 8 or 9 days, after operation) being 3.5 per cent. In 36 operations performed on the right side the operative mortality was 19.4 per cent. Bull considers the operation to be more dangerous when right-sided. The deaths recorded by him were due to various causes, such as pneumonia, endocarditis, &c., but in several instances in which no conclusive evidence was gained at the autopsy he thinks that death was due to increased absorption of toxins from the collapsed lung.

The above facts are here repeated only in general support of the theory

that right-sided collapse has usually a less favourable outlook than left-sided collapse; that there is some ground for thinking that this may be true of artificial pneumothorax in particular may be gathered from the following observations: Rivièrè (12), discussing the lung circulation in collapse therapy, refers to the commonly expressed belief that the collapsed lung is comparatively empty of blood, the untreated lung being hyperaemic; it has been suggested by some that to this hyperaemia is due the favourable effect of compression upon diseased foci in the opposite lung. If this view is correct, it may explain the difference in the results between right-sided and left-sided artificial pneumothorax. One might expect to find contralateral disease more frequent in the left lung after a right-sided pneumothorax on account of the pressure exerted upon the right side of the heart, with consequent impairment of the pulmonary circulation. Rist (13), in a recent paper on the respiratory excursions of the mediastinum, describes a remarkable contrast between the action of the heart on the normal side and its greatly exaggerated action on the pneumothorax side. When the heart is separated from the lung by gas, the heart-beats become considerably amplified; this is observed after expiration, and is most marked at the beginning of the inspiratory phase. Before the end of inspiration the heart again comes into contact with the lung, and the heart-beats are reduced in amplitude, becoming again normal. He concludes that the normal contact of the heart with the lungs acts as a brake to the systolic contraction. It would seem that this might have some relation to the progress of events in pneumothorax when one considers the possible effect of the above movements upon the circulation, and especially, in the case of right-sided pneumothorax, upon the pulmonary circulation and therefore upon conditions in the left (untreated) lung. Rist has been unable to make out any change in the rhythm or mode of contraction of the heart, and finds the electro-cardiogram constantly normal, nor does he observe any disturbance in the normal respiratory variation of the blood-pressure. It is, however, conceivable that permanent effects might be produced through the pulmonary circulation in cases of right-sided pneumothorax with a considerable degree of collapse maintained over a sufficiently long period of time (cf. Case I).

In those cases of artificial pneumothorax of which the writer has had experience the condition of the opposite lung has varied considerably, and evidence has constantly been sought for as to the precise state of affairs at any given time on the relatively good side, evidence which is seldom forthcoming, and which, it is believed, should constitute one of the most salient points in the choice and subsequent management of cases. Reference has already been made earlier in this paper to the distinction between contralateral disease and contralateral activity, the importance of which appears to be under-estimated in most of the writings on the subject of bilateral disease. In 1,122 cases, reported by twenty-four American observers, Sachs (14) gives a table of incidence of various complications occurring in the course of artificial pneumothorax treatment in which extension of disease in the opposite lung was noted in 58 instances out

of a total of 237 complications (i.e. 24.5 per cent.), but no details are given as to the exact condition of the lung or the circumstances under which the trouble arose. In a recent report to the Medical Research Council (10), in the passages dealing with bilateral disease as a contraindication, stress is laid chiefly upon the anatomical extent of disease in the better lung, although some of the contributors emphasize the distinction between activity and quiescence. One of the observers, in reply to the questionnaire, gives details in regard to the different kinds of disease in the other lung, and in one communication only is there any reference in this connexion to mediastinal displacement.

Some valuable information is given by the Matsons and Bisailon (9) in a review of the end results of 600 cases treated by artificial pneumothorax over a period of twelve years. These authors have divided their cases into groups according to the extent and character of the disease, detailed attention being paid to the 'status of the non-compressed lung', of which their classification, as follows, is worthy of notice :

- '1. Essentially negative (physical signs and X-ray evidence).
- '2. Deep peribronchial infiltration (chiefly X-ray evidence).
- '3. Disseminated bronchogenic caseous extensions, characterized by the presence of localized caseous pneumonic, broncho-pneumonic, or disseminated confluent tuberculous infiltrations in the perihilar regions or dependent portions of lung parenchyma.
- '4. Active fibro-caseous infiltration.
- '5. Quiescent fibro-caseous infiltration.'

The last two they consider as being the result of aspiration of bacilli-laden sputum. Although they find a relationship between the status of the collateral lung and the results of artificial pneumothorax treatment, they consider that if recovery takes place it does so more often in spite of whatever disease either existed or appeared later on the opposite side, and that if death occurs it is more frequently from causes other than extension of disease to the collateral lung or its progression in that lung if already established there. This last observation of these authors appears to the writer to have a very important bearing upon the majority of artificial pneumothorax work at the present time, and it raises the hope that the relationship in question may in future be better understood and utilized as a basis for greater technical accuracy in treatment.

Discussion of Results.

A close comparative study of the details of the six cases which are given as an appendix at the end of the paper may, it is hoped, throw some light upon the main points of discussion in regard to the behaviour of the untreated lung during the course of treatment by artificial pneumothorax.

Case I was of fairly chronic type, with a history of two attacks of pleurisy. In spite of this there was no trouble from adhesions, and from the X-rays it is evident that there was a flexible mediastinum. The manometric readings are, on

the whole, fairly constant, and in spite of the introduction on occasions of very large amounts of air, especially during the earlier period of the treatment, at no time was an excessive positive pressure maintained, the maximum reading immediately after a refill being +4, +10 (i.e. a mean pressure of +7), the majority of after-pressures being considerably lower than this. It must be remembered, moreover, that readings taken some hours after a refill are frequently lower than those taken at once. The distress experienced after the introduction of 1,200 c.c. on 29.9.23 was evidently due to cardiac embarrassment resulting from excessive pressure (screen examination at this time showed considerable displacement of heart and mediastinum). In the previous April there had been a remarkable degree of pleural bulging, as shown in the accompanying plate (Plate 18, 10.4.23), but there was then no marked distress, only slight dyspnoea on exertion; it must be remembered, however, that at this time the patient was still being kept in bed. From the X-ray appearances at this stage it will be apparent that considerable pressure must have been exercised upon the untreated (left) lung, without, however, any immediately untoward results. From October 1923 onwards the amounts given were considerably reduced and lower pressures maintained, with the result that the patient's weight, which had begun to drop somewhat, increased again, and she continued to make excellent progress up to August 1924, at which time she was apparently at her best. It is important to note that it is at this period that the X-ray (Plate 19, 22.8.24) first shows definite evidence of infiltration in the middle zone of the untreated (left) lung, although no physical signs of activity were apparent on clinical examination. The attack of influenza in February 1924, which caused a good deal of anxiety for about a week, apparently produced no ill effects upon the lung, and her progress continued uninterrupted until January 1925, when she began to complain of increased fatigue, and there was some loss of weight. After the second attack of influenza, in February 1925, she developed definite physical signs in the opposite lung for the first time since the beginning of the treatment, and from this point onwards she began to do badly, and tubercle bacilli again appeared in the sputum. Perhaps the most striking feature of the case is the fact that at the time when the maximum pressure must have been exerted on the untreated lung no indication of contralateral disease, either clinical or radiological, was present, the first evidence of change in the opposite lung, as indicated by X-rays only, not appearing until nearly a year afterwards, and then without any corresponding clinical signs of activity, these not being manifested until after the lapse of a further six months. It is, however, a matter for question whether or not the compression may have had a harmful effect upon the collateral lung and prepared the ground for the reactivation of a focus of disease of which the final determining factor was the occurrence of the influenzal attack in the early part of 1925.

Case II was of much more acute type than the preceding one; the need for artificial pneumothorax appeared very much more urgent, and treatment was undertaken almost immediately. The patient was a native of southern Ireland, with a low immunity and racial predisposition to tuberculosis; the history as regards onset of manifest disease in her case was a short one, the spread of active disease being apparently very rapid. The X-ray appearances of the opposite lung were good (Plate 20, 23.10.23), and for fifteen months her progress under pneumothorax treatment was uninterrupted up to the time when a severe attack of influenza of gastro-intestinal type caused a serious set-back, and signs of disease appeared in the opposite lung. It will be noticed that the apex of the treated lung in this case was fibrous and adherent (Plate 20, 21.1.24), and from the fact that much smaller amounts of air were given at the refills, with very high resulting positive pressures, it may be inferred that the pneumothorax cavity was small, the mediastinum relatively fixed, and the compression of the

collateral lung inconsiderable. The occurrence of the influenzal attack towards the end of February 1925 is possibly an important factor in relation to the development of active contralateral disease.

Case III illustrates a definitely acute type of pulmonary tuberculosis. This girl was a difficult subject for pneumothorax treatment, temperamentally unstable, and often hard to manage from a nursing point of view. The X-ray appearances (Plate 21, 4.3.24) as regards the opposite lung were less favourable than in Cases I and II, the middle zone being very suspicious, but no extensive definite mottling was seen in the original film, nor were there any abnormal physical signs on admission. In view of the evidence of rapid caseation in the right lung, artificial pneumothorax appeared to hold out the only hope of arresting the disease. The amounts of air introduced and the pressures maintained were high, and under ordinary circumstances would not have been justified, but it was thought that, unless fairly complete collapse of the lung were obtained, there was not much prospect of reducing the toxæmia and of maintaining the temperature at a steady level, especially in view of the patency of a large cavity in the middle zone. In spite of the compression of the opposite lung by the mediastinal displacement, considerable improvement in the symptoms resulted from the pneumothorax, and the temperature was reduced to a more or less normal level, except for occasional rises. Cauterization of adhesions was undertaken because it was thought that the exacerbations of fever and the persistence of tubercle bacilli in the sputum were due to the patency of the cavity, which could not be collapsed owing to the lung being held by stout adhesions to the thoracic wall. The diminution in size of the cavity and the increase in the degree of collapse of the lung following the cauterization are well illustrated in the accompanying plate (Plate 21, 15.9.24 and 20.10.24), which also shows the corresponding increase in compression of the opposite lung, to which the sudden appearance, within a few days, of signs of active disease on that side appeared undoubtedly to be due.

Case IV furnishes a good example of the initial difficulty of decision as to suitability for pneumothorax treatment. From the history of the few months prior to his admission it was obvious that this boy was going downhill, but the physical signs on the relatively good side indicated a definite extent of disease, and from the X-ray appearances (Plate 22, 28.6.23) it was evident that there had been fairly considerable infiltration of the right lung. For this reason a good deal of doubt was felt at first as to the wisdom of collapsing the left lung, and the decision to attempt this was based firstly on the absence of moist sounds on the right side, the physical signs being mainly those of fibrosis, and secondly on the extremely bad prognosis as judged by the sudden increase of symptoms and rapid deterioration in the patient's general condition, as well as by the bad family history. From the rather high positive pressures obtained, and the X-ray appearances after the first few refills (Plate 22, 11.7.23), it was seen that there was irregular collapse owing to apical and basal adhesions, the absence of any gross displacement of the heart and mediastinum being explained by this fact. In spite of the instability of the patient's condition during the earlier part of his stay in the sanatorium, his ultimate improvement was most satisfactory, and from the details of the Frimley report it is evident that the non-appearance of active disease in the collateral lung was largely if not entirely due to the fixation of the mediastinum, in which the development of fluid played an important part. From the subsequent progress after leaving Frimley it is obvious that prognosis for the future must necessarily be somewhat guarded and that this patient will need the most careful watching and protection, but the result up to date has been most encouraging, and throws a good deal of light upon the scope of pneumothorax therapy and upon the vexed question of initial choice of cases.

Case V represents the most chronic type of all the six examples. She was, moreover, of a naturally placid disposition, and amenable to any course of treatment. The physical signs on the right side suggested slight activity, but it was mainly owing to the X-ray appearances (Plate 23, 23.10.23 and 3.1.24) that I was unwilling to induce a pneumothorax. In the interval between the first and second X-ray examinations the infiltration had increased appreciably in extent, which seemed still further to contra-indicate an attempt to collapse the left lung, and it was only as an experiment, and at the urgent request of the relations, who were anxious for a trial of this treatment, that I consented to undertake it. The one favourable point was the chronicity of the disease and the probability from the history of repeated attacks of pleurisy that the case was one of the adhesive type, and that therefore excessive contralateral pressure from gross mediastinal displacement was unlikely. Study of the pressure readings appears to confirm this view. The occurrence of a spontaneous pneumothorax, due to rupture of the lung from tearing of adhesions, was an unfortunate accident, but although for a period of over a week the patient's condition was desperate, and it was feared that she would succumb to shock, yet the final result was satisfactory, and it is interesting to note that the very complication which almost caused the patient's death was in all probability the means ultimately of saving and prolonging her life. After absorption of the fluid effusion which succeeded the spontaneous pneumothorax, her progress was unhindered (cf. also *Case IV*). The displacement of the heart at the time of the rupture of the lung was extreme, but radiographic appearances of the mediastinum could not be obtained, as the patient's condition did not admit of her being moved. The final X-ray (Plate 23, 3.6.24) does not indicate much 'crowding' on the opposite side, but the precise amount of compression of the right lung during the acute phase could not be determined.

Case VI is of considerable importance as furnishing an example of a difficult and thoroughly unsuitable subject presenting almost every contra-indication for artificial pneumothorax. There was active disease in both lungs; the patient was a nervous and unreasonable woman, unaccustomed to discipline of any sort, capricious over her diet, and extremely difficult to nurse. The pneumothorax was undertaken as a last resource in view of the apparently hopeless prognosis, so often associated with puerperal tuberculosis. When she left the hospital, afebrile, and able to take moderate walking exercise, it was pointed out to her relations that the ultimate prognosis was bad, owing to the amount of disease in the uncollapsed lung which was likely to flare up later on, but the improvement in her general condition and the relief of symptoms over a period of some months were such as would seem to justify the course taken. In this case, as in others, it will be observed that although fairly large amounts of air were introduced, the resulting positive pressures were not excessively high, and the mediastinal displacement was not such as to cause more than moderate and possibly beneficial compression of the untreated lung, the auscultatory signs on the right side having diminished considerably, and the activity of the disease being apparently much less after three months of treatment.

The increasing effusion on the pneumothorax side will be noticed in the last two X-rays (see Plate 24, 13.2.25 and 31.3.25) taken shortly before she went to Frimley.

The apparent paradox seen in the results in Cases IV to VI as compared with those in Cases I to III is not easy to explain. Is it due to faults of technique or is it due to the different powers of resistance in the individuals? The latter question can hardly be answered at present, but the former may be investigated in the light of these cases, and it is hoped that the notes given in

this paper may have furnished suggestions and ideas as to the lines on which such investigation should proceed. It would appear that so far as technique is concerned the two most important factors to be borne in mind in connexion with the development of contralateral disease are, first, the exact condition of the untreated lung, and, secondly, the degree of compression to which this lung is subjected by mediastinal displacement. The chief difficulty in regard to the former is the lack of sufficiently precise information afforded by the methods of examination at present in use. In spite of modern advances in radiology, and the assistance, invaluable as it is, from this source, the best possible skiagrams are difficult of interpretation, even by the most expert, and may at times be misleading. The information gained from physical signs alone is at best somewhat crude, and the correlation between clinical medicine and radiology, in this country at least, falls far short of that which should be the ideal of every large institution. It is outside the scope of this paper to enter into questions which fall within the province of the clinical pathologist, but it is possible that the precise 'status' of a lung, from an artificial pneumothorax point of view, may be one of those problems in immunology for which, in addition to other means of investigation, we should invoke the aid of the laboratory, and attention may be called to recent work of Bannerman (16) and others on blood-plate counts in tuberculous and other infections.

As regards pressure from mediastinal displacement the chief conclusion to be drawn is that this is one of the main potential sources of trouble, and that in any case of doubt it is better to keep on the safe side of lower pressures. The main factor in the transmission of pressure to the opposite side is flexibility of the mediastinum. Nitsch (15) describes two thin and flexible spots in the mediastinum which are especially prone to transmit an effect to the opposite lung after pneumothorax. One of these is situated anteriorly, behind the sternum, the other posteriorly, in the neighbourhood of the large vessels. It is interesting to note that in all the cases in which X-ray shows evidence of infiltration in the untreated lung the characteristic appearances are first observed in the middle zone. Rivière (12) considers that the mediastinum should never be displaced as far as the mammary line, however low the pressure which leads to its displacement, and thinks that too high a pressure may cause a permanent stretching and displacement which may remain an embarrassment to the opposite lung even after a return to lower pressures (cf. Case I). He refers to 'the increased tolerance of the patient which will permit a gradual rise to pressures which are needless, undesirable, or even dangerous', and says, 'It must be recognized that a pressure which causes no immediate discomfort to the patient may yet be a source of ultimate danger by displacement and embarrassment of other organs, and particularly of the opposite lung'. There are, it must be noted, instances in which without any doubt the patient appears to do better on higher pressures, even when there is considerable displacement of heart and mediastinum; in one case (not quoted in this paper), in which the writer has kept up a pneumothorax for over three years, the higher pressures were maintained in response to the

expressed wish of the patient, an educated intelligent woman, who insisted that she always felt better and was freer from symptoms under these conditions. No untoward results were ever observed so far as the condition of her other lung was concerned. The writer has further found that he has gained more satisfactory results by raising the pressures in the earlier stages of treatment, within the limits of the patient's tolerance, until a fairly complete degree of collapse has been obtained. In many instances where smaller refills have been given and the intrapleural pressure maintained at a figure below the zero line, the degree of collapse attained has been less, the return to a condition of apyrexia delayed, and the general improvement in the patient's condition less obvious. It further may be remarked that the effect upon patients of a tangible result, within a reasonably short space of time from the initial induction, is not without significance from the psychological aspect, the importance of which should not be under-estimated.

It is difficult to say what are the precise effects of acute infections occurring during the course of pneumothorax treatment. In Cases I and II it will be noticed that the first really serious set-back followed closely upon an attack of so-called influenza. The question naturally arose at the time as to whether this was in reality a manifestation of tuberculous activity, but in both cases careful inquiry into the mode of onset and symptoms, and the fact of both these patients having been definitely exposed to the risks of a prevalent epidemic of undoubted influenza, made this point fairly clear. That the occurrence of any acute secondary infection in a patient already suffering from quiescent pulmonary tuberculosis is a serious matter, fraught with danger, is well known, and in those undergoing artificial pneumothorax treatment it is especially to be feared. In the after-care of those who have had a pneumothorax induced in a hospital or sanatorium, and whose treatment is being continued at home, the avoidance of such infections so far as possible is a point on which it is necessary to lay some emphasis, and this may well be taken into account when advising such patients in regard to their future environment in those instances in which circumstances render possible some choice in the matter.

Reports of Cases (abridged), with Details of Intrapleural Pressures.

Case I. I. G. M., female, aged 18. Admitted February 1923, with a history of pleurisy three years ago, and a second attack in December 1922; since the last attack she had cough, dyspnoea, and occasional night-sweats. T.B. found in sputum. *Physical signs:* on the right side dullness with bronchial breathing and crepitations over the upper half of the chest in front and behind; on the left side slight dullness below the clavicle and in the supraspinous fossa; occasional crepitations just above the spine of the scapula. *X-ray* (Plate 18, 19.2.23): 'Heart small, vertical, and with mediastinum drawn to the right. *Right lung:* upper and middle zones infiltrated; fibrosis and suggested excavation in infra-clavicular region. *Left lung:* no definite infiltration noted, but increased streakiness.' Artificial pneumothorax induced on 7.3.23, and treatment kept up for two

years. 14.5.23: discharged from hospital afebrile, no cough, no sputum, attended out-patient department for refills. 15.9.23: weight 7 st. 9 lb. Physical signs of large pneumothorax; about this time she began to experience distress from excessive pressure; this, however, disappeared after reduction of the pressure, no ill effects being apparent. In February 1924 she had a typical attack of genuine influenza and was taken into hospital for a few days; her temperature, which had been 101° F., fell to normal and the refills were continued as before; she was apparently none the worse for this attack. 15.3.24: slight morning sputum with a little colour. No physical signs of disease on the left side. *X-ray* (Plate 19, 22.8.24) showed definite alteration in the appearance of the left lung (especially in the middle zone) suggesting infiltration, and different entirely from the appearances due to 'crowding' from pressure transmitted from the pneumothorax side. 10.1.25: not quite so well; slight loss of weight; complaining of undue fatigue. 21.2.25: admitted to hospital febrile. Had been laid up at home for the past week with influenza; a few fine crepitations below left clavicle. 27.3.25: T.B. again present in sputum. Temperature still irregular. *X-ray* (Plate 19, 10.1.25) shows re-expansion of the right lung and considerable alteration in the appearance of the untreated (left) lung, which the radiologists report as 'extensive infiltration in the middle zone'. The last refill was given on 21.4.25, after which the pneumothorax treatment was discontinued, the following comment being made in the notes: 'Comparison of the last three radiograms, August 1924, January 1925, and May 1925, does not show any very considerable difference; there appears to be more infiltration on the left side in the skiagram of January 1925 than in that of the preceding August, but between the last two (January and May of 1925) there is little to choose, although three refills were given in the interval. The last rise of temperature, i.e. from May 15, since when the evening temperature has been above 100° F., appears to coincide with her getting up for six hours a day. From all the clinical data it appears that there is increasing activity of centrally situated disease in the contralateral lung, and that further refills will only aggravate this by increasing the compression on this side beyond the limit of safety. It appears wiser to discontinue treatment at present with a view to the possible induction of "selective collapse" on the left side at a later date when re-expansion of the right lung has occurred.'

Case I.

Date.	Pressures before.	Amount injected. c.c.	Pressures after.
7. 3.23	... - 11 - 7	350	... - 8 - 6
8. 3.23	... - 9 - 6	550	... - 5 - 2
10. 3.23	... - 6 - 3	750	... - 2 + 2
14. 3.23	... - 6 - 5	1000	... - 2 + 1
17. 3.23	... - 4 - 1	500	... + 3 + 5
24. 3.23	... - 6 + 1	800	... + 6 + 9
31. 3.23	... - 5 + 4	550	... 0 + 8
21. 4.23	... - 4 + 4	750	... + 4 + 10
9. 5.23	... - 6 + 1	600	... - 2 + 6
23. 5.23	... - 5 + 1	700	... + 1 + 5
23. 6.23	... - 2 - 8	700	... + 1 + 4
4. 7.23	... - 7 - 0	760	... - 1 + 4
28. 7.23	... - 11 - 5	1000	... - 2 + 2
18. 8.23	... - 12 - 6	980	... - 2 + 1
1. 9.23	... - 10 - 4	1050	... - 2 + 2
15. 9.23	... - 8 - 2	950	... - 2 + 3
29. 9.23	... - 7 - 2	1200	... + 2 + 8
13.10.23	... - 5 + 1	670	... - 2 + 4
27.10.23	... - 6 - 2	450	... - 2 + 10
10.11.23	... - 6 - 2	250	... - 3 - 0
24.11.23	... - 7 - 4	300	... - 4 - 1
8.12.23	... - 7 - 3	300	... - 4 - 0

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Date.	Pressures before.		Amount injected.		Pressures after.	
			c.c.			
22.12.23	...	- 10 - 5	...	600	...	- 4 - 1
5. 1.24	...	- 7 - 3	...	600	...	- 2 + 1
19. 1.24	...	- 7 - 3	...	250	...	- 4 - 1
6. 2.24	...	- 7 - 3	...	420	...	- 4 - 1
23. 2.24	...	- 11 - 5	...	600	...	- 4 + 1
15. 3.24	...	- 8 - 5	...	620	...	- 1 + 1
5. 4.24	...	- 8 - 4	...	600	...	- 1 + 3
26. 4.24	...	- 6 - 3	...	450	...	- 2 + 1
17. 5.24	...	- 8 - 4	...	500	...	- 2 + 1
31. 5.24	...	- 7 - 3	...	400	...	- 2 + 1
21. 6.24	...	- 9 - 6	...	360	...	+ 2 + 4
(weight increasing)						
16. 7.24	...	- 8 - 5	...	600	...	- 2 + 1
26. 7.24	...	- 16 - 6	...	500	...	- 3 + 2
16. 8.24	...	- 10 - 5	...	500	...	- 2 + 1
6. 9.24	...	- 9 - 5	...	500	...	- 3 - 0
27. 9.24	...	- 9 - 5	...	600	...	- 3 + 1
18.10.24	...	- 8 - 4	...	450	...	- 2 + 1
8.11.24	...	- 11 - 6	...	470	...	- 3 - 0
29.11.24	...	- 10 - 5	...	550	...	- 1 + 2
20.12.24	...	- 10 - 7	...	420	...	- 4 + 2
17. 1.25	...	- 11 - 7	...	600	...	0 + 3
25. 2.25	...	- 10 - 4	...	620	...	+ 2 + 3
26. 3.25	...	- 8 - 6	...	800	...	- 2 - 0
21. 4.25	...	- 14 - 8	...	660	...	- 4 + 4

Case II. N. S., female, aged 24. Admitted October 1923. Slight haemoptysis. T.B. found in sputum. History of cough for the last three months after a febrile attack. Physical signs of active disease (caseation and cavitation) involving the whole of the right lung. In the left supraspinous fossa slight bronchophony and a few crepitations (? conducted from opposite side). *X-ray* (Plate 20, 23.10.23): 'Heart and mediastinum displaced to the right side. *Right lung*: fibrosis excavation and thickened pleura in upper and middle zones, infiltration of lower zone. *Left lung*: no definite infiltration of lung tissue seen.' Artificial pneumothorax begun on 1.11.23. The patient made very good progress, complete collapse of the lung being obtained except at the apex. T.B. disappeared from the sputum. By the end of March 1924 she was up for the whole day and was transferred to Frimley from April to August. She had then put on weight, had no cough or sputum, and was able to return to her work as a clerk, and continued in excellent health up to February of 1925, when she had a very severe attack of influenza of gastro-intestinal type, this being to some extent prevalent in London at the time. 7.3.25: physical signs of slight general bronchitis, but no clinical evidence of any definite infiltration of the opposite lung. She was admitted to hospital for observation, when, after a further interval, crepitations were heard below *both* clavicles and fine rhonchi all over both lungs; temperature irregular, evening rise 99° to 100° F. Numerous râles developed over the whole of the right side. 24.4.25: 'absolute rest' ordered. Towards the end of May it was decided to discontinue the refills entirely, as the X-ray showed definite evidence of extensive involvement of the opposite lung.

The temperature charts (Charts 1 and 2) illustrate the rise of temperature due to spread of active disease in the untreated lung, with subsequent drop to normal after the pneumothorax had been discontinued. The subsidence of the fever corresponds presumably with the decompression of the treated lung. The circles on May 12, 16, and 18 mark the inversions of the morning and evening temperatures.

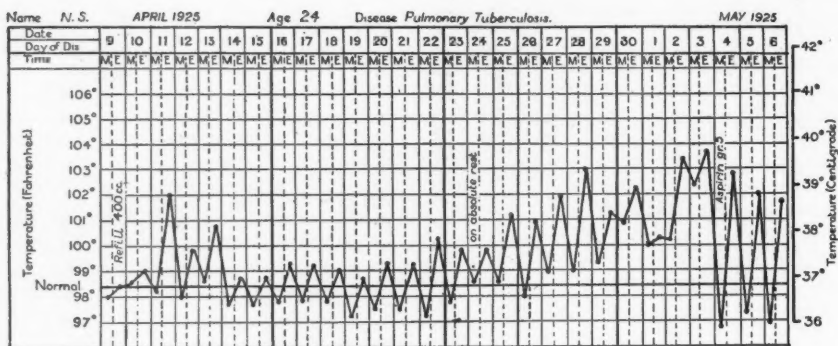


CHART 1.

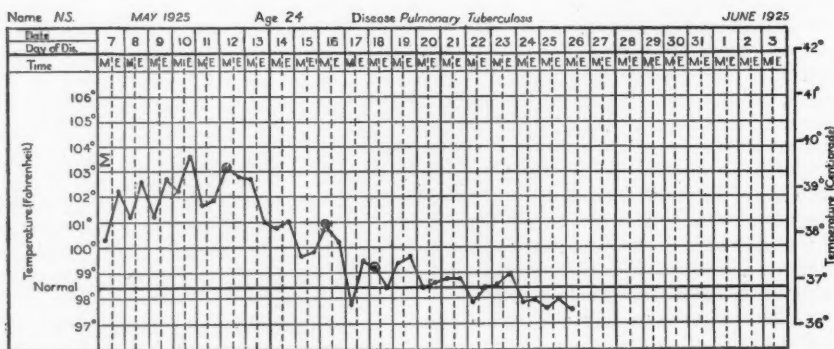


CHART 2.

CONTRALATERAL DISEASE IN PNEUMOTHORAX THERAPY 195

Case II.

Date.	Pressures before.			Amount injected.			Pressures after.		
				c.c.					
1.11.23	- 8 - 5	300	0 + 1
2.11.23	- 5 - 0	300	+ 2 + 5
4.11.23	- 8 - 3	300	+ 8 + 13
7.11.23	- 5 - 2	400	+ 22 + 26
10.11.23	- 4 - 1	400	+ 16 + 20
14.11.23	- 1 + 1	450	+ 18 + 22
17.11.23	+ 8 + 10	400	+ 16 + 18
24.11.23	+ 1 + 6	400	+ 20 + 28
1.12.23	- 3 + 2	500	+ 20 + 26
12.12.23	- 2 + 1	500	+ 17 + 20
22.12.23	+ 2 + 4	400	+ 16 + 20
2. 1.24	+ 1 + 7	500	+ 28 + 32
16. 1.24	- 2 + 2	450	+ 30 + 36
2. 2.24	- 5 + 2	480	+ 30 + 36
16. 2.24	- 4 + 3	300	+ 8 + 20
5. 3.24	- 7 + 1	400	+ 29 + 31
22. 3.24	- 6 - 2	400	+ 29 + 31
8. 7.24*	- 5 (mean pressure)	200	+ 17
29. 7.24*	- 4 ³ "	200	+ 17
18. 8.24*	- 4 "	250	+ 16
6. 9.24	- 10 - 1	300	+ 28 + 30
27. 9.24	- 16 - 3	300	+ 30 + 32
18.10.24	- 10 - 0	150	+ 2 + 8
15.11.24	- 12 - 5	400	+ 30 + 33
13.12.24	- 12 - 4	390	+ 26 + 30
10. 1.25	- 12 - 2	300	+ 14 + 18
10. 3.25	- 11 - 7	450	+ 21 + 23
4. 9.25	- 10 - 4	400	+ 12 + 14

* Report of last three pressures at Frimley.

Case III. M. G., female, aged 15. Delicate-looking girl. Previous history of several acute infectious diseases (measles, diphtheria, &c.). Admitted February 1924 with cough and frequent vomiting. Considerable fever, chart showing the 'inverted type' of pyrexia. Night-sweats and much dyspnoea, sputum abundant and containing T.B. Physical signs most marked at right lower lobe, where there was evidence of cavitation; infiltration of upper and middle lobes. No abnormal physical signs were present on the left side. *X-ray* (Plate 21, 4.3.24): 'Heart small. *Right lung*: extreme infiltration; appearances of excavation of middle and lower zones. *Left lung*: suspicious infiltration of middle zone.' Artificial pneumothorax begun on 8.3.24. Considerable improvement occurred; the cough and vomiting became less and the temperature came down almost to normal, but was always somewhat unstable. Early in October it appeared that progress was being retarded, possibly owing to the presence of adhesions. As the *X-ray* (Plate 21, 15.9.24) showed a long adhesion from the lower pole of the lung to the diaphragm, and also a short stout mass of adhesions in the upper part, preventing collapse of the cavity, it was thought that this patient was a suitable case for cauterization of adhesions by Jacobaeus's method. On 8.10.24 she was examined with the thoracoscope and the adhesions clearly demonstrated. Both adhesions were divided with the galvano-cautery; the patient stood the operation well and little or no shock was experienced. 11.10.24: condition satisfactory; slight febrile reaction on the two days following operation; considerable surgical emphysema, but no undue discomfort; a small refill was given. The last refill was on 25.10.24; the temperature chart was now showing very irregular fever, and marked physical signs were apparent on the left side of the chart, suggesting softening and excavation at the apex. On the right side the physical signs were those of a large pneumothorax. After this date the patient got rapidly weaker

CONTRALATERAL DISEASE IN PNEUMOTHORAX THERAPY 197

rib. Since that date his progress was uninterrupted. 3.12.24: weight 8 st. 2½ lb. General condition excellent. Physical signs suggested fibrosis of lung with thickened pleura and complete obliteration of pleural cavity on the left side. Up to the present time he has continued well except for occasional trivial symptoms. *X-ray* (Plate 22, 3.6.25) showed no increase in the density of the right lung, which appeared, if anything, clearer on comparison with the original skiagram before the pneumothorax.

Case IV.

30.6.23 Initial attempt. 100 c.c. of air introduced, apparently in a pocket. A second puncture was unsuccessful, no oscillation of the manometer being observed.

Date.	Pressures before.		Amount injected.		Pressures after.	
1.7.23	- 10 - 2	- 6 + 10
(Needle introduced in second left intercostal space, about 3 in. from middle line.)						
2.7.23	- 8 + 2	- 4 + 4
4.7.23	- 6 + 2	- 4 + 6
7.7.23	- 8 + 4	+ 2 + 10
11.7.23	- 6 + 4	+ 8 + 12
19.7.23	0 + 6	+ 8 + 12
28.7.23	- 4 + 6	+ 6 + 14
8.8.23	- 4 + 4	+ 5 + 10

Case V. B. A. S., female, aged 18. Admitted October 1923. Previously in a sanatorium for three months and discharged as she was making no progress. Cough and expectoration since December 1922. Had had several attacks of pleurisy before that. On examination, physical signs of extensive disease in left lung with cavitation; on the right side behind dullness with bronchial breathing and crepitations above the spine of the scapula. *X-ray* (Plate 23, 23.10.23): 'Heart and mediastinum displaced to the left; left side of diaphragm fixed. *Left lung*: fibrosis and excavation; diffuse opacity suggesting thickened pleura. *Right lung*: compensatory emphysema; infiltration of upper and middle zones.' The appearances seen in the *X-ray* were such, and the clinical findings in the right lung so definite, that collapse therapy was thought to be contra-indicated, and she was treated for some time with Dreyer's vaccine without any resulting improvement. After the last injection the temperature rose to 101° F., and she continued to show marked irregular pyrexia. The vaccine was stopped and the question of artificial pneumothorax treatment was again discussed. A further *X-ray* (Plate 23, 3.1.24) showed 'Increased opacity of left side of chest: apparently more infiltration of right lung than at previous examination'. Artificial pneumothorax begun on 16.1.24. No difficulty experienced, although there must have been numerous adhesions. Only five refills had been given when she suddenly developed a spontaneous pneumothorax, apparently the result of rupture of an adhesion and tearing of the substance of the lung. For about a week she remained in a critical condition owing to shock; the distress was relieved by repeated removal of air at intervals. Ultimately the hole in the lung became closed, a large pleural effusion developing. No further interference was attempted, and in the course of time the fluid was absorbed. 1.6.24: up about four hours a day and afebrile. 13.8.24: transferred to Frimley, where she continued to do well. 14.1.25: weight 9 st. 5½ lb. General condition good. Slight morning cough and sputum in small amount; T.B. still present. Physical signs of fibrosed left lung with thickened pleura; a few fine dry crackling sounds audible in front. On the right side bronchial breathing above the spine of the scapula; a few occasional crepitations audible below the right clavicle. From this time onwards she continued to do well, the physical signs in the chest remaining very much the same, and up to date her condition is satisfactory, appetite good, and weight stationary.

Case V.

Date.	Pressures before.			Amount injected.			Pressures after.		
					c.c.				
16.1.24	- 9 - 8	...	400	- 6 - 1	
17.1.24	- 8 - 4	...	600	+ 4 + 5	
19.1.24	- 6 - 2	...	500	+ 3 + 5	
23.1.24	- 5 - 1	...	700	+ 9 + 10	
29.1.24	- 2 + 2	...	800	+ 15 + 17	

Case VI. V. R., female, aged 33. Admitted June 1924. History of cough and expectoration for 6-8 months, much worse since her confinement, three months before admission. T.B. present in sputum. Physical signs of extensive disease in both lungs: dullness and bronchial breathing over the greater part of the chest in front and behind, with loud consonating râles over the whole of the left lung; on the right side, finer râles in front and behind over the upper half of the chest. *X-ray* (Plate 23, 30.6.24): 'Heart and mediastinum drawn to the left. *Left lung*: fibrosis and excavation in upper zone, general infiltration in the rest of the lung. *Right lung*: some infiltration at apex and irregularly throughout lung.' Artificial pneumothorax treatment was considered to be out of the question. The patient was put on 'absolute rest', but after about six weeks the temperature was still irregular and showed no signs of settling. In view of the apparently hopeless outlook, it was determined to attempt a partial pneumothorax on the left side as a last resource; this was done on 23.8.24, with the immediate results which are shown in the accompanying charts. After some weeks she was allowed up, and was finally able to return home on 29.11.24. On 29.2.25 she was readmitted to hospital, as she had been having slight fever at home and was nervous and difficult to manage, but although the temperature was now irregular it settled again after rest in hospital. The physical signs of activity on the opposite side appeared much less than before the beginning of pneumothorax treatment, and she was well enough towards the end of May to be transferred to Frimley, where she remained for some weeks before returning home. Fluid developed on the left side latterly and at Frimley the refills were discontinued.

The temperature charts illustrate: Chart 3, irregular pyrexia during the first four weeks after admission, unaffected by treatment with 'absolute rest'. Chart 4, state of temperature at a later period, and effect upon temperature of collapse of the worse lung.

Case VI.

Date.	Pressures before.			Amount injected.			Pressures after.		
					c.c.				
23. 8.24	- 7 - 6	...	300	- 5 - 3	
24. 8.24	- 6 - 4	...	400	- 4 - 2	
26. 8.24	- 7 - 2	...	400	- 4 - 0	
29. 8.24	- 7 - 3	...	400	- 4 - 0	
2. 9.24	- 7 - 5	...	600	- 5 - 2	
6. 9.24	- 6 - 3	...	600	- 2 + 1	
10. 9.24	- 8 - 2	...	700	0 + 3	
17. 9.24	- 7 - 1	...	550	- 1 + 3	
24. 9.24	- 6 - 2	...	520	- 1 + 1	
1.10.24	- 5 - 1	...	550	- 1 + 3	
11.10.24	- 4 + 1	...	600	0 + 4	
23.10.24	- 8 - 2	...	620	- 2 + 2	
8.11.24	- 8 - 2	...	600	- 3 + 2	
26.11.24	- 10 - 4	...	750	- 3 + 1	
20.12.24	- 16 - 6	...	550	- 9 - 1	
10. 1.25	- 16 - 4	...	620	- 7 + 4	
28. 2.25	- 15 - 6	...	500	+ 2 + 6	
13. 4.25	- 12 - 7	...	600	+ 26	

Pressure gradually dropping to about + 10 when needle was removed.

CONTRALATERAL DISEASE IN PNEUMOTHORAX THERAPY 199

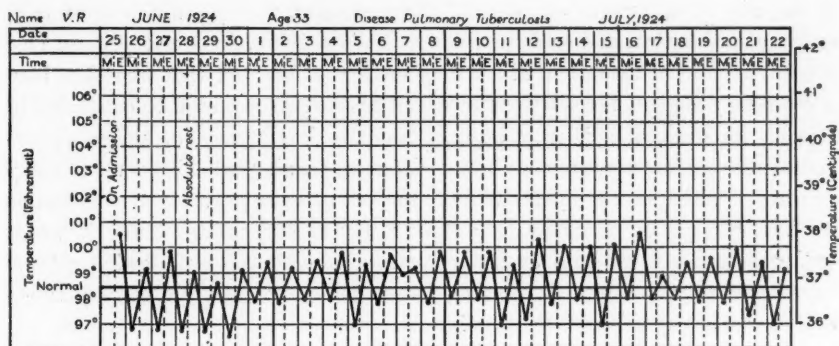


CHART 3.

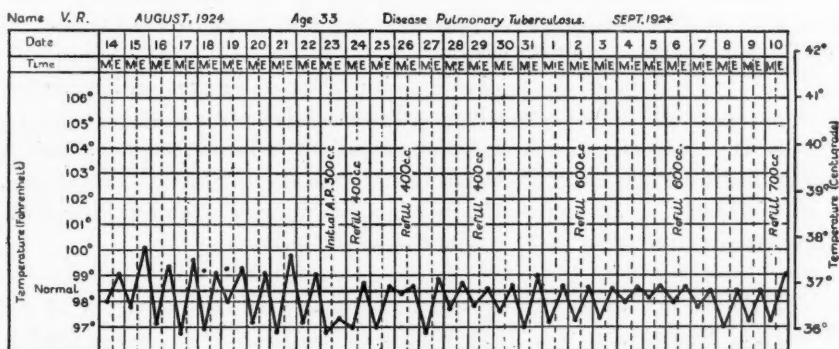


CHART 4.

Conclusion.

Sufficient has been said to emphasize the need for more detailed knowledge as regards those aspects of artificial pneumothorax therapy which have been under consideration, and which, in the writer's opinion, have not yet received the full amount of attention which they merit; it is hoped that what has been written may suggest the direction in which investigation should be conducted in future. In conclusion it may be said that the development of active contralateral disease is an occurrence which depends, in all probability, upon many factors, of which our comparative ignorance at present prevents the perfection of the technique in the management of many of our cases. While it would be unreasonable to attempt any more precise deductions, the following general statements may, perhaps, be permitted in respect of cases of pulmonary tuberculosis treated by artificial pneumothorax:

1. As regards the condition of the relatively sound lung, the activity or otherwise of the pathological process is of vastly greater importance than the anatomical extent of the morbid changes.

2. Acute cases present more urgent need for artificial pneumothorax than do chronic cases, but are more liable to give trouble owing to the development of active contralateral disease.

3. There is some ground for believing that the side upon which an artificial pneumothorax is performed may be of importance as regards the prognosis, and that in right-sided cases the outlook is less favourable than in those in which the collapse has been effected on the left side.

4. There is no definite criterion of safety in regard to contralateral pressure, and it is possible that excessive pressures may sometimes be the cause of ill results entirely remote in their effects.

5. The condition of the mediastinum is a factor of the greatest importance, its relative fixity determining to a large extent the degree of contralateral pressure.

6. The occurrence of acute infections, especially influenza, may be a serious factor in determining an exacerbation of active disease in the uncollapsed lung, and this should, so far as possible, be taken into account when considering the future environment of artificial pneumothorax patients.

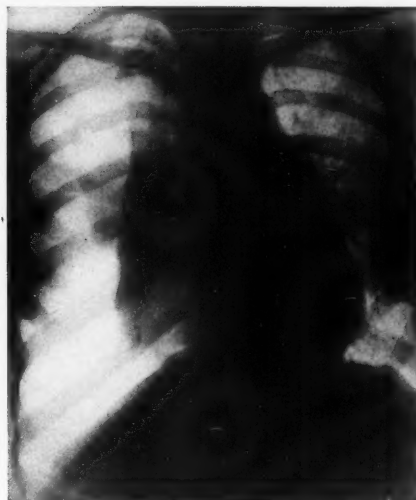
I should like to express my gratitude to two of my colleagues at the Brompton Hospital: to Dr. Cecil Wall, who has afforded me every possible facility as regards access to cases, and to Dr. Stanley Melville, without whose valuable radiological work and courteous assistance in the interpretation of skiagrams this paper would never have been written. I am also indebted to Sir John Rose Bradford for kindly reading the rough draft, and especially to Professor Arthur J. Hall for invaluable help in revision and correction.

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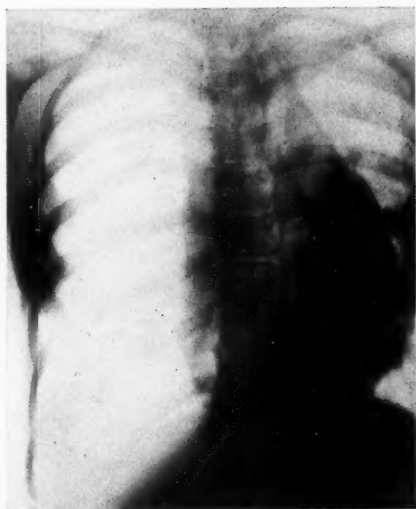
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Case I. 19.2.23.



Case I. 20.3.23.

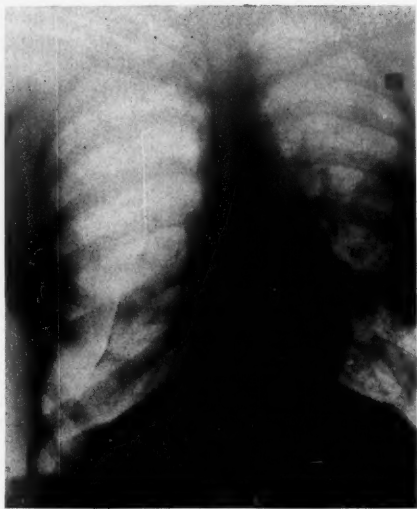


Case I. 10.4.23.



Case I. 17.8.23.

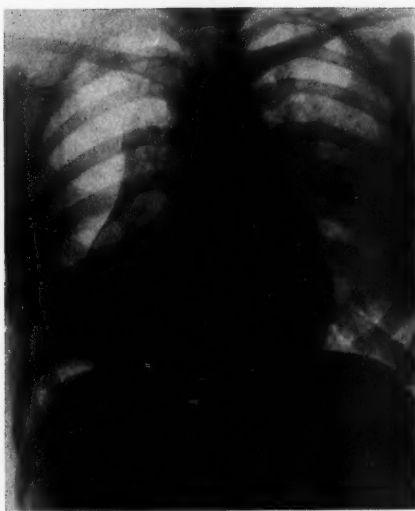




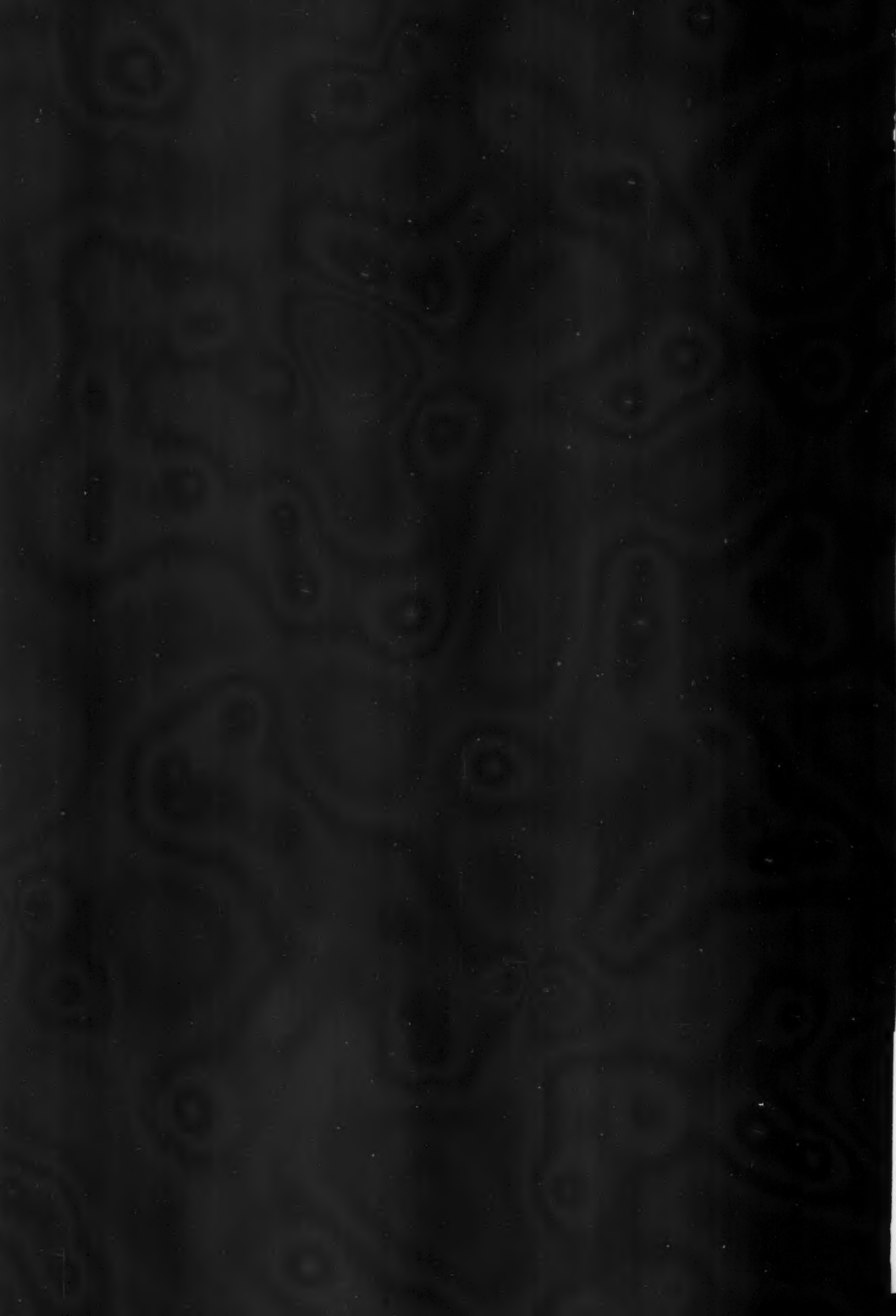
Case I. 22.8.24.



Case I. 10.1.25.

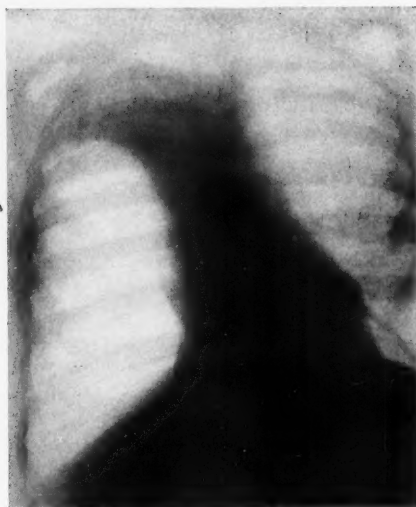


Case I. 21.5.25.

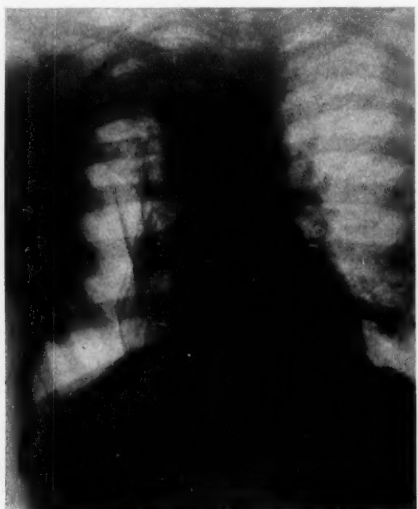




Case II. 23.10.23.



Case II. 21.1.24.

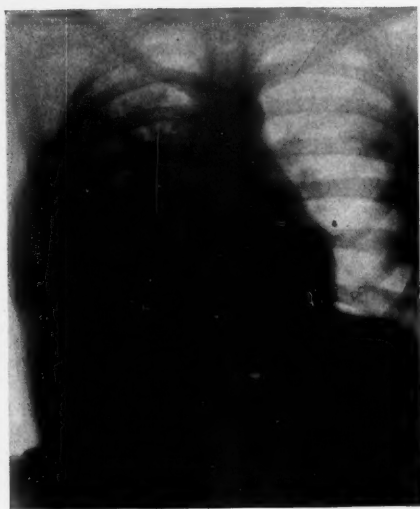


Case II. 9.2.25.

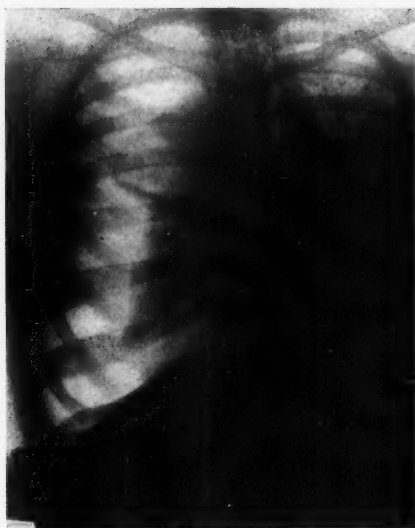


Case II. 17.4.25.





Case III. 4.3.24.



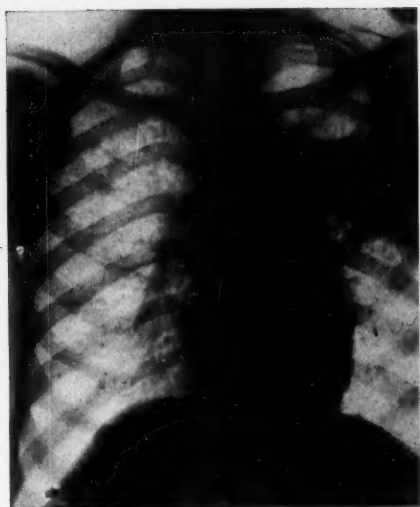
Case III. 3.4.24.



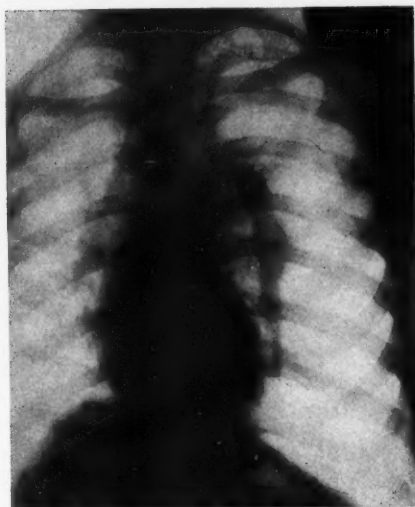
Case III. 15.9.24.



Case III. 20.10.24.



Case IV. 28.6.23.



Case IV. 11.7.23.

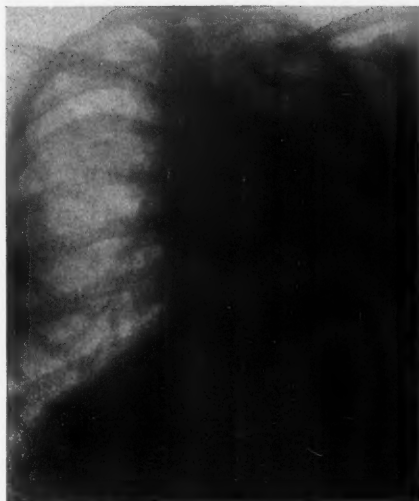


Case IV. 3.6.25.

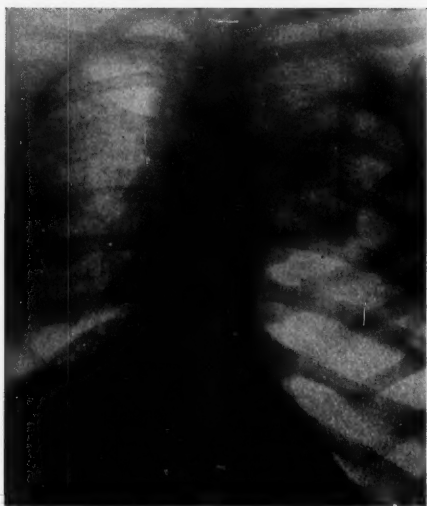




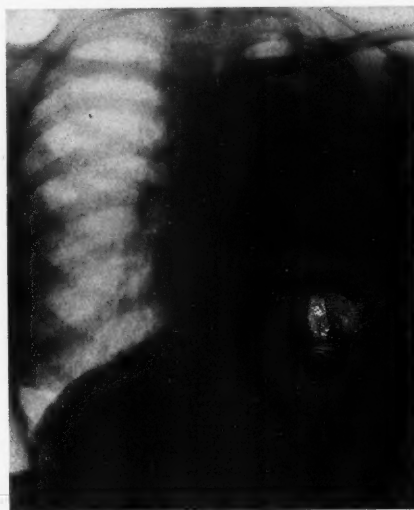
Case V. 23.10.23.



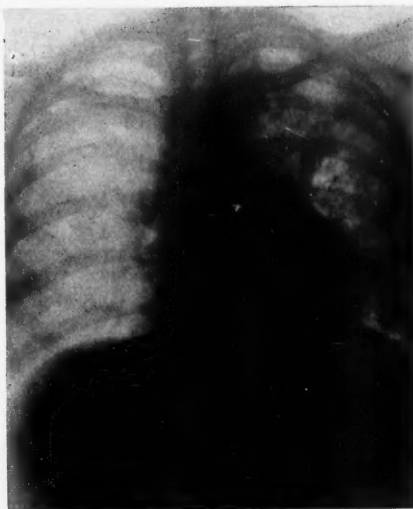
Case V. 3.1.24.



Case V. 31.1.24.

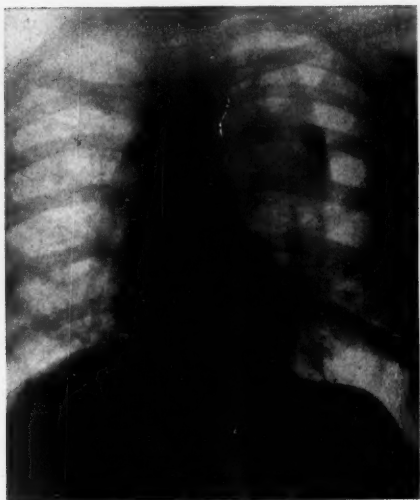


Case V. 3.6.24.



Case VI. 30.6.24.





Case VI. 30.9.24.



Case VI. 27.11.24.



Case VI. 13.2.25.



Case VI. 31.3.25.



NERVE IRRITATION AND AORTIC LESIONS AN EXPERIMENTAL STUDY¹

By R. CUNLIFFE SHAW

With Plates 25-27

THE remarkable tissue changes that are associated with certain nervous diseases have led to the postulation of a trophic or controlling influence in the nervous system over the structures it supplies. Investigators working with this theoretical principle as a basis have studied experimentally the effects of nerve decontrol on the tissues, more especially in relation to the vascular system. Research, primarily undertaken with respect to mixed nerves distributed in the limbs, has later concentrated on the sympathetic paths to the peripheral blood-vessels, but in a few cases similarly distributed nerves in the splanchnic division of the autonomic system have been extirpated. Following the same hypothesis, clinical research has been directed to the study of the changes in the vascular system in distal parts of a limb, where the nerve-supply has been exposed to an irritative lesion more proximally located; as, for example, in cases of cervical rib or as a sequel to gunshot injury. The outcome of these two lines of inquiry has been the continuous accumulation of evidence in support of the tissue-governing powers exercised by the nervous system, and the serious pathological changes consequent upon the loss or perversion of this influence. The experimental evidence demonstrating the morbid changes resultant from the dissociation of this mechanism, both for vessels supplied by the somatic and the splanchnic distributions of the sympathetic, is at once strikingly decisive. On the other hand, total nerve-lesions simulating the results of operative procedure are infrequent, which is obviously a serious disadvantage to the practical application of such discoveries; otherwise the association of nerve-lesion and vascular change is fully indicated by the clinical findings. The vital difference lies in the artifact being dependent on a total abolition of nervous communications, whereas the morbid lesion is irritative long prior to its possible culmination in loss of neural conductivity. The problem which concerns this thesis was, therefore, to induce vascular changes through the medium of irritative nerve-lesions, the investigation on these principles being conducted with respect to the cardio-aortic nerve-supply. Before proceeding to a discussion of the practical work it is of the first importance to review the outline of the evidence on which rests the cogency of the basal hypothesis.

¹ Received June 26, 1925.

The Results of Previous Investigations.

Fraenkel, in 1896, working on the subject of trophic changes in *tabes dorsalis*, investigated the vascular lesions in these cases. He found, in young subjects, long before the age of senile degeneration, that the anterior tibial vessels showed overgrowth of the intima and medial hypertrophy. He then proceeded to cut the sciatic nerve in a series of dogs and rabbits, from all of which he obtained similar lesions in the blood-vessels.

In 1897 Cehanovic furthered these observations by severing only the sympathetic nerves and examining the effect on the vascular system. These he summarized in their sequence as follows :

1. Dilatation of the veins and elongation and thickening of the nuclei in the tunica media.
2. The capillaries dilate.
3. The lymph vessels dilate.
4. The connective tissue near the blood-vessels exhibits a hyperplasia of its cells.

Lapinski conducted experiments on the cervical sympathetic, which he severed in rabbits, and observed the effects on the arteries of the ear. Out of fourteen cases seven showed definite pathological lesions; in some it consisted of rapid atrophy of the media at certain points, and thickening of the intima; in others the media underwent hypertrophy and the vasa vasorum in most cases showed changes. In 1908 von Bechterew summarized the effects of nerve section on the blood-vessels as resulting in the increase of elastic tissue in the intima and media with an associated muscle hypertrophy in the latter. Up till this period most of the experimental work had been conducted on nerves associated with the peripheral blood-vessels. The next step was to determine whether similar effects could be produced in the large arteries in the splanchnic distribution of the autonomic system. Manouélian furthered this side of the inquiry, publishing his results in 1913. This investigator, pursuing the researches of Metchnikoff on the intestinal toxication theories of arteriosclerosis, was surprised to find the lesions in the vasa vasorum were generally insignificant and incapable of exciting the more serious changes in the main vessel. Thus, in a number of human aortae so strongly impregnated with lime salts that it was necessary to resort to decalcifiants, he found that the vasa vasorum in the adventitia and media were undamaged—'autour de la plaque et même en pleine plaque athéromateuse il existait des vaisseaux perméables avec un endothélium très net et des globules rouges dans leur lumière'. An admirably coloured plate illustrates this point. The apparent insignificance of the lesions in the vasa vasorum determined his investigation on the role of the nervous system in the causation of these changes. Manouélian found that in dogs there is a fairly constant nerve filament proceeding from the solar plexus to supply the abdominal aorta close to the origin of the left renal artery. He operated on four animals, removing this nerve between two strong forceps; they were allowed

to recover, one being kept for twenty days and the others for two months. On post-mortem examination in all four cases atheromatous plaques were found in that part of the vessel supplied by the nerve.

In a fifth animal the thorax was opened under artificial respiration, the pericardium incised, and a nerve filament to the pulmonary artery removed. At the autopsy sixty-five days later a sclerosed plaque was found in that part of the vessel deprived of its nerve-supply. His coloured plates show that the lesions excited consisted of hyperplasia of the intima and media with secondary degenerations. In conclusion, he considers that nerve-lesions (*arrachements*) are capable of exciting arteriosclerosis, and that histological investigation shows that the pathological changes excited bear a marked resemblance to those found in this disease in human beings.

On the clinical side there has been a corroborative growth of evidence. T. Wingate Todd in 1913 described the changes in the radial artery that accompany cervical rib. In the adventitia he found no change, in the media a hyperplasia, and in the intima a hypertrophy of the elastic tissue accompanied by a proliferation of the endothelium; the veins showed hypertrophy of the muscle coat. The same investigator in another paper advanced the view that changes in the wall and lumen of blood-vessels due to endarteritis obliterans may be dependent on lesions of the nerve-supply to the same, and that such changes in the vessels are the exciting cause of the trophic lesions in the skin and deeper tissues. Finally, he considered that interference with the trophic nervous supply of the vascular system has an important bearing on arteriosclerosis. More recently these conclusions have been amplified by the researches of Prof. J. S. B. Stopford on the effects in the vascular system of irritative lesions in the peripheral nerves the sequelae of gunshot injuries. One of these cases may be cited in exemplification of the type of lesions and subsequent pathological changes. The patient, aged 23 (negative Wassermann), had been shot through the left thigh in 1916. The leg was removed in 1918 on account of contractures and paralysis of muscles. Examination showed that the internal and external popliteal nerves were involved in dense fibrous tissue, whilst the popliteal artery and vein were patent. Microscopical investigation of the distal part of the posterior tibial artery revealed a 'slight uniform proliferation of the intima'. The elastic lamina and endothelium were intact and the media showed no definite change. On the other hand, the dorsalis pedis and plantar vessels presented far more advanced lesions. The intima was markedly proliferated, but not uniformly; the endothelial layer and the elastic lamina were disintegrated. The muscle-cells of the media showed undoubted signs of degeneration.

Professor Stopford in summarizing the evidence says, 'There is strong reason to conclude that irritative nerve-lesions can produce changes in the walls of the arteries supplied by the affected nerves . . . the contention held by Todd that vascular changes precede trophic lesions is strongly supported by the clinical observation of these cases.' With this as a basal theory, an experimental investigation was carried out on the cardio-aortic nerves, having as an objective

the production of pathological changes in the aorta through an irritant acting slowly on its nerve-supply.

The Experimental Investigation.

It was primarily decided to produce an experimental arteriosclerosis in rabbits by means of adrenalin injection, so as to possess a standard with which to compare the changes excited by neural irritation, it being generally considered that the lesions provoked by the adrenalin method are comparable with the arteriosclerotic changes which normally occur in these animals.

The mode of production of arterial lesions by adrenalin, as practised by Josuè and followed by Pearce and Polettini, is to inject a few minims of a 1 in 1,000 solution of adrenalin hydrochloride into a vein at intervals of one or two days, the experiments being continued for six or eight weeks.

The pathological conditions that result may be summarized as follows:

1. Focal areas of degeneration and necrosis of the smooth muscle-fibres in the media. No macroscopical lesion is evident at this stage.
2. The extension of these changes so as to involve the greater part of the middle zone of the media. The elastica shows swelling and fragmentation of the fibres, whilst fat droplets appear in these degenerative areas.
3. Following twelve to fifteen injections distortion of the artery due to the formation of local plaques renders the changes macroscopical. Microscopical section shows the formation of calcified areas, but it is noted by Pearce that 'distinct atheroma with ulceration was seldom seen'.
4. These changes were accompanied by marked proliferation of the sub-intimal tissue, but endothelial proliferation was not found to any great degree. These processes coincided with the necrotic areas in the media.

In the present instance this method was carried out on four animals. The injections of 1 in 1,000 adrenalin hydrochloride were generally given into a vein in the ear, but on several occasions they were administered intramuscularly, the gluteal regions being selected. When the intravascular route was used, the dose was approximately 4 minims, but in the case of gluteal injections the dose was increased to 8 minims.

Three of the animals were put on adrenalin on January 8, the first two of these dying on March 17 and 19 respectively—that is, after periods of 68 and 70 days. During this time they received sixteen injections each; in these the average interval of the doses was about 4.3 days. Six of these were given intramuscularly, the remainder into a vein in the ear. The third animal died on March 28, having had seventeen injections during an approximate dosage interval of 4.6 days. Like the first two, it received six intramuscular injections.

In the fourth animal the experiment was started on February 5, and it was examined on April 13, having had twelve injections in this period, making an average dosage interval of 5.6 days.

The effects of these injections were manifested by the general prostration of the animals, accompanied by rapid respiration and heart-beat; although the latter would be partly due to fright, the former was quite marked. The animal generally laid down in the side of the cage with the hind-legs extended. Recovery, however, was rapid in all cases, the rabbits appearing outwardly normal after an hour.

In the cases of the first three rabbits, death followed progressive asthenic symptoms. In that of the fourth, it was due to a bilateral fibrinous pleurisy with serous pericarditis.

The results of the post-mortem and histological examinations of the aortas were as follows:

1. *Rabbit. Ref. No. 855.* Experiment started 8.1.24. Died 19.3.24.

Post mortem. No microscopical lesion of the aorta; the intima of the vessel appeared quite smooth and the cross-section normal.

Histology. Microscopical section showed no evidence of change in any of the aortic coats.

2. *Rabbit. Ref. No. 856.* Experiment started 8.1.24. Died 17.3.24.

Post mortem. No signs of any gross lesion in the aorta.

Histology. No evidence of any change in the intima. In the media the muscle-cells appeared normal. There was a suggestion of slight hypertrophy in this coat.

3. *Rabbit. Ref. No. 857.* Experiment started 8.1.24. Died 28.3.24.

Post mortem. No macroscopical lesion in the aorta.

Histology. The muscle-cells of the media showed signs of degeneration and separation, especially in the middle zone. The intima showed a proliferation of the connective tissue elements; these appeared to be necrotic areas in the hyperplasia. There was no plaque formation.

4. *Rabbit. Ref. No. 864.* Experiment started 5.2.24. Died 13.4.24.

Post mortem. Bilateral fibrinous pleurisy and serous pericarditis. The aorta appeared normal.

Histology. The aorta showed no histological changes.

From the above experiments it is clear that in only one were there changes which would compare with those described by Poletini, Pearce, and others. Perhaps the injections were made at too frequent intervals, otherwise the dosage, the route adopted, except on six occasions, and the number of injections were precisely the same. The one example which showed pathological lesions sufficed to illustrate the nature of the early stages of experimental arteritis in rabbits, and as this was all that was required from the adrenalin injection, the particular investigation was not farther pursued.

The three cases that failed to show any definite morbid process may be accepted as controls for the later experiments; their value from this standpoint is all the more increased in view of the animals having been subjected to a known arterial irritant and for having been confined throughout the course of the experiment. They will be referred to later.

The means for the production of irritation in the cardio-aortic nerves fall into two groups, according to the mode of application:

1. Irritation carried out directly in connexion with these nerves through an operation.
2. Means applied externally.

Chief of the latter is electrical stimulation, and this will be discussed first. The objective was to irritate either the sympathetic or vagal paths by the passage of an electrical current of approximately constant strength. For this purpose a two-volt accumulator and a Du Bois-Reymond induction coil and copper electrodes were employed, the induction coil being used at a constant position with an accumulator of the same voltage for all cases. The usual procedure was to moisten the skin of the animal with a little saline solution and apply the wire electrodes along the course of the vagus and cervical sympathetic, the upper one just below the jaw and the lower near the sternum on the left side. At other times the electrodes were both applied to the cervical spine, the upper one just below the occiput and the lower about the upper dorsal region, whilst on other occasions one electrode was wound round the left foreleg and the other applied to the cervical spine. This method was employed if the animal proved refractory.

As regards the strength of the stimulus, it was surprising to notice that the same degree of irritation produced similar responses in the different animals, the position of the induction coil necessary to excite a painful degree of stimulation being, generally speaking, the same in each instance. The equity of the stimulus could then be gauged to a nicety, the strength used being such as not to invoke signs of pain, but allow the animals to sit perfectly still. When commencing these experimental stimulations, the rabbits were always very restive, but they soon settled down so as not to require restraint after one or two occasions.

The animals showed very definite general signs of response to the different stimuli. Thus, if the vagal path was affected, there was a readily observable slowing of the respiration. In one animal in particular this response was very striking—the respiration would be inhibited for a moment, followed by slow and deep respiratory movements. The heart was likewise markedly inhibited, this being all the more apparent on account of the previous excitement attendant on the removal from the cage having quickened it. In all cases, the application of the electrodes to the cervical spine, or to this and the limb, were accompanied by rapid heart-beat and respiration. The eyes became especially prominent, and very definitely so if the strength of the current were increased.

The duration of stimulation was on an average about ten to fifteen minutes, but on a few occasions it was as long as thirty minutes, and twice, forty-five and sixty minutes respectively in one case (No. 876). The animals bore the long applications very well, sitting quite still and appearing as if hypnotized by the humming of the induction coil. After being returned to the cages, they appeared but little the worse, eating carrots with avidity. The results may now be considered.

1. *Rabbit. Ref. No. 865.* Experiment started 5.1.24. Died 19.4.24. This animal was subjected to sixteen stimulations, giving an average of 6.8 days between the applications.

Post mortem. The right ventricle dilated, the muscle thin and brown, the left ventricle pale and contracted. The mitral valve thickened. No gross lesions in the aorta; some slightly raised areas of whitish discoloration in the intima which contrasted with the general colour of the coat.

Histology. Section of the aorta stained with haemalum and eosin. The central zone of the media showed a focus of degeneration of muscle and the proliferation of connective tissue cells. The smooth muscle-fibres were shrunken and widely separated near the diseased focus and faintly stained. The intima showed signs of early hyperplasia at several points.

2. *Rabbit. Ref. No. 876.* Experiment started 5.1.24. Died 23.5.24. This animal was subjected to twenty-four stimulations, thus averaging 5.75 days between the applications.

Post mortem. There were several large and many small nodular thickenings of the intima in the arch of the aorta and the upper part of the descending thoracic aorta, which entirely faded away a little above the diaphragm. The plaques had a linear distribution. Cusps of the aortic valve were markedly sclerosed.

Histology. Haemalum and eosin section. The intima showed very pronounced hyperplasia occurring in sharply defined plaques, but there was also a slight, generally distributed, proliferative change. The new cells composing these nodules appear to consist principally of stellate connective tissue cells; although it is difficult to speak with absolute certainty, there does not appear to have been much hyperplasia of the endothelium. The deeper parts of the intima showed necrotic changes; this was proceeding at different foci in the plaques, which were separated by non-degenerated strands of connective tissue, passing vertical to the plane of the circular muscle in the media. In the latter, the muscle-cells are undergoing definite necrosis at certain points, but the principal change is intimal.

Section stained with Sudan III. There was very definite fatty deposition in the necrotic areas of the intima; masses of cholesterol crystals also appeared in these foci. Fat also appeared in fine globules in the wandering connective tissue cells in the spaces between the proliferated intimal tissue outside the boundaries of the plaques.

Rabbit. Ref. No. 877. Experiment started 5.1.24. Died 1.6.24. This animal was subjected to the same number of stimulations as No. 876.

Post mortem. No apparent pathological lesion.

Histology. Aorta section stained with haemalum and eosin. The intima showed an early diffuse proliferation of its cellular elements. The muscle-fibres of the media appeared to show early degeneration in parts, the fibres being poorly stained and shrunken, but on the whole this change was not very definite, the intimal lesions being the principal feature.

The foregoing results show that pathological change had occurred in every case, and that the earliest degree was present in the animal that had been the least stimulated (No. 865), it having died thirty days before the second pair, after living 102 days from the commencement of the experiment. It will be recalled that Manouélian discovered a calcareous plaque in the pulmonary artery sixty-five days after the operation, but that in his case the lesion was total, whereas here it was only irritative. A more advanced degree of intimal proliferation and a more diffuse medial change had occurred in No. 877, whilst No. 876 showed a still more pronounced intimal change, the hyperplasia having reached

the necrotic stage. The possibility of this animal being already subject to arteriosclerosis has to be borne in mind, and the matter is discussed with that of the controls to the other experiments. It is interesting to note, however, that this rabbit was the one on which the longest stimulations were practised.

Death resulted in each case after gradually increasing asthenic symptoms, the animals falling off their food and becoming weaker and thinner. In none of the cases were any acute lesions found, such as might account for sudden fatal termination.

Lastly, in one animal the adrenalin and electrical stimulation methods were practised successively. The rabbit was started with adrenalin injections on March 24, and received seven doses, the last on May 5. These were given intramuscularly and averaged about 6-8 minims each. After May, electrical stimulation was carried out as in the other experiments. In all, there were fourteen stimulations, the animal being finally killed on December 15. The following lesions were present in the aorta:

Rabbit. Ref. No. 966.

Post mortem. Five atheromatous plaques in the first part of the aorta, two being located close to the origin of the innominate artery.

Histology. Haemalum and eosin section. Marked proliferation of the intima and degeneration of the smooth muscle of the media.

Orcein section. Areas of proliferation of elastic tissues in the intima and subintimal zones with fragmentation of the larger elastic fibres of the media at corresponding points.

Sudan III. A slight fatty infiltration at different foci of the intima; no marked degeneration.

The electrical experiments, and, indeed, any procedure applied externally with a view to excitation of particular nerves, is under the disadvantage of being indirect in its method and uncertain in its mode of action. The possibility of complicating factors, such as might arise from stimulation of the endocrine system, renders the results open to criticism.

It was, therefore, decided to endeavour to irritate the cardio-aortic nerves directly, not by gross traumatism, but through the medium of some slowly acting irritant, thereby obviating a possible concurrent stimulation of tissues that might compromise the conclusions. Two operative procedures were devised to effect these changes and both proved satisfactory in practice.

In the first method, the mode of irritation was by exposure of the nerves to the air, whilst in the second the irritant was scar-tissue. As a matter of fact, the end results as regards the nerves were much the same after either procedure—that is, fibrous tissue formed around and embedded them in a tight scar.

Now, as to the way in which the first procedure was carried out. This was primarily effected by simply exposing the nerve on the surface of the skin, by dissecting it from its bed and under-running a skin-flap; this was found to result in rapid drying, necrosis, and rupture, and was consequently quite unsuitable for the proposed experiments. This method was, therefore, modified by wrapping the nerve in a tubular skin-flap, which kept it moist and protected

from external injury, whilst allowing exposure to air and irritation from fibrous adhesions. The steps by which this was carried out may now be described.

The animal having been anaesthetized with ether and laid in the supine position, a longitudinal incision was made over the anterior triangle. The superficial cervical fascia was incised and the interval between the infrahyoid muscles and the sternomastoid sought, the deep cervical fascia opened, and the carotid artery with the surrounding nerves defined. The particular nerve required having been identified, it was separated from its surroundings by gentle probe dissection and lifted to the surface. To effect this without undue tension on the nerve it was generally necessary to incise the infrahyoid muscles and bring the nerve through the slit. The skin of the right- or left-hand margin of the wound was then closely shaved and two parallel incisions, about 2 cm. apart and 1.5 cm. long, made into this margin at right angles to the line of the wound at a level with the exposed nerve. Then a small rectangular flap was fashioned, the fore margin of which was transfixed with a stout catgut suture and carried beneath the nerve, the needle emerging well beyond the margin of the opposite side of the wound, thereby effectively drawing the flap between the nerve and contiguous structures. The skin margins were then sutured. In the cases treated on this plan, the final result, on post-mortem examinations, was a small fibrous scar firmly enclosing the nerve; the submerged skin undergoing a quiet aseptic necrosis and replacement by fibrous tissue. In no case was there any suppurative inflammation.

In a few cases, an attempt was made to obviate the formation of adhesions by the interposition of Cargile membrane between the nerve and the margins of the skin-flap, but however successfully this was accomplished at the operation, the end result was always the same: a firm knot of fibrous tissue round the nerve. In the second method, the immediate objective was to produce scar-tissue around the nerves. For this purpose the particular nerve selected was surrounded by an isolated piece of muscle cut from one of the infrahyoid muscles, but in one case a piece of a human pectoralis major was used. The nerve, having been separated from the contiguous structures, was carefully wrapped in the muscle for about 3 or 4 cm., the margins of the latter being securely stitched together and the whole enclosed with Cargile membrane. The small gap in the infrahyoid muscle was stitched with a fine 0-00 catgut and the wound closed. These cases healed by first intention, and the ultimate result was the same as in the preceding, a firm mass of fibrous tissue forming. The next considerations were the nerves selected for irritation and the anatomical position of the irritant. In view of the absence of any detailed description of the nerve-supply to the aorta in rabbits, a brief review of the nerve distribution to this structure may be excused.

Anatomical.

On the left side the nerves that supply the aorta are the sympathetic, the vagus, and the depressor.

The sympathetic on the left gives off a constant branch from the superior cervical ganglion, which descends close to the inner side of the carotid artery and commonly breaks up into a plexus of fine branches just above the arch of the aorta over the origin of the left carotid, some of the filaments passing over the aorta to the superficial cardiac plexus and thence to the heart, others proceeding to the deep cardiac plexus behind the aorta. From both plexuses and directly very fine filaments can sometimes be traced into the walls of the vessel about its first and second parts.

A small branch to the deep cardiac plexus can sometimes be found arising from the middle cervical ganglion. From the inferior cervical and the ganglion stellatum several small filaments can be constantly found passing to the aorta. On the right side, the superior cervical branch can be traced to the deep cardiac plexus, and occasionally a distinct filament can be followed as far as the aortic wall just above the heart.

The vagus on the left side gives off a cardiac branch low down in the neck which passes to the superficial cardiac plexus within the arch of the aorta; on a few occasions I have noted a separate filament from this twig to the aorta close to the origin of the innominate artery. On the right side, a fine branch can frequently be traced from the vagus near the origin of the recurrent laryngeal to the deep cardiac plexus—occasionally a twig passed directly into the wall of the first part of the aorta.

The depressor. This delicate nerve arises from the vagus and the superior laryngeal, passing down the neck close to the former and ending in branches to the arch of the aorta.

It was decided to attempt the stimulation of these three nerve paths separately. In all, thirty-two operations were performed, distributed as follows: Twenty-two on the vagal path; five on the sympathetic; and five on the depressor.

Firstly, with regard to the vagus, eighteen animals survived the operation, giving a mortality of 18.1 per cent. From the survivals five must be discounted through a possible fallacy arising, due to their deaths from pneumonia and pleurisy with pericarditis. This leaves thirteen cases free from fallacies arising through acute intercurrent disease. Out of these, ten showed positive results which are described hereafter. In this series one (No. 954) had both vagi exposed, in the others the left vagus only was operated on.

Secondly, with respect to the cervical sympathetic, all the five animals recovered from operation. There were four positive results, out of which number one (No. 947) had both superior cardiac cervical sympathetics irritated, the others only that on the left side.

Finally, with regard to the depressor, only three animals survived the

operation, giving a mortality of 40 per cent. The two animals that died expired immediately following the disturbance of this nerve.

There were two positive results.

Although the several cardio-aortic nerves were separately subjected to operation with a view to determining which particular fibres were chiefly instrumental in the production of the lesions, no reliance can be safely placed on these facts because in all cases there were adhesions involving the other structures, including the nerves in the proximity of the particular one selected, which in some cases were very dense; consequently, the irritation must necessarily have affected all three paths in each case.

In no instance was the physiological conductivity of the nerves tested before the animal was killed.

The positive results may now be described:

The Results of Vagal Irritation.

1. *Rabbit. Ref. No. 879. Operation 8.5.24. Died 28.5.24. Exposure of the left vagus, which was wrapped round with a piece of human pectoral muscle and the wound closed.*

Post mortem. No gross pathological change in the aorta.

Histology. Section stained with haemalum and eosin. The intima showed a very early diffuse proliferation of cells, which appear to be principally of connective tissue origin. The muscle-fibres of the media showed early degenerative changes.

2. *Rabbit. Ref. No. 895. Operation 18.6.24. Died 27.7.24. Exposure of the left vagus, which was placed in a tubular skin-flap.*

Post mortem. The base of the aorta was intensely congested, the rosy colour extending up the first part of the aorta nearly as far as the innominate artery. One or two nodular thickenings were present in this area.

Histology. Section stained with haemalum and eosin. The intima showed a sharply defined conical plaque, composed principally of proliferated connective tissue cells, which had become organized into fibrous trabeculae and appeared to be undergoing a hyaline change, the nuclei being few and widely separated, and the individual fibres appeared to be fused in places into an undifferentiated substance. The adjacent intima also showed proliferative changes of a minor degree. In the media there appeared to be a corresponding hypertrophy, but no definite degenerative signs.

Section stained with Sudan III showed no fatty infiltration or degeneration.

3. *Rabbit. Ref. No. 941. Operation 25.6.24. Killed 20.10.24. Exposure of the left vagus, embedded in a muscle-flap from the infrahyoid group and surrounded with a skin-flap.*

Post mortem. Nodular thickening in the aorta near the origin of the innominate artery.

Histology. Section stained with haemalum and eosin. There was a diffuse proliferation of the intima and subintimal tissues, with the deposition of many dark-coloured pigment granules amongst the endothelial cells. The media showed some hypertrophy corresponding to the most advanced intimal change.

Orcein section. The elastic tissue in the intima and subintimal layers showed a hyperplasia corresponding to the thickened areas.

Sudan III section. No evidence of fatty change.

4. *Rabbit. Ref. No. 942. Operation 5.6.24. Killed 24.10.24. Exposure of the left vagus, which was surrounded by a piece of detached rabbit-muscle and a skin-flap.*

Post mortem. No definite plaque formation; areas of whitish discoloration which showed the changes described below.

Histology. Haemalum section. There was definite proliferation of the intima, mainly composed of connective tissue cells. The smooth muscle-cells of the media did not appear normal; their staining was irregular, and some showed signs of disintegration, and there was thickening in this coat at one point, corresponding to more pronounced intimal change.

Sudan III section. No evidence of fatty degeneration.

Orcein section. There was a very pronounced increase of elastic tissue in the intima, accompanied by fragmentation of the fibres.

5. *Rabbit. Ref. No. 946. Operation 30.4.24. Killed 13.11.24. Exposure of left vagus, which was embedded in a detached piece of muscle and surrounded by a skin-flap.*

Post mortem. Plaque formation in the first part of the aorta near the innominate artery.

Histology. Haemalum and eosin section. There were proliferative changes in the intima, but no gross degeneration; the section, unfortunately, missed the plaques, which were accidentally destroyed in slitting open the aorta.

Orcein section. There was a slight increase of elastic tissue in the intima. Many fat globules were to be seen in the intimal layer. *Note.*—It is probable that these changes were far more pronounced in the plaque zone that was destroyed, the sections being taken from the vicinity of this region.

6. *Rabbit. Ref. No. 949. Operation 28.8.24. Killed 21.11.24. Exposure of left vagus, which was surrounded by a tubular skin-flap.*

Post mortem. Several plaques in the first part of the aorta, especially near the orifices of the innominate and carotid arteries.

Histology. Haemalum and eosin section. The intima in this section showed a diffuse proliferation of its cellular elements, many of which were of an angular or stellate form. The media showed a hyperplasia at points corresponding to the most prominent intimal change.

Orcein section. The elastic tissue showed a definite hyperplasia in the intima; many of the small fibres appeared to be undergoing degeneration with fragmentation. A similar proliferation of the elastica was seen in the inner layers of the media at points corresponding to the intimal change. These fibres also appeared to be undergoing fragmentation.

Sudan III section. No fatty change.

7. *Rabbit. Ref. No. 952. Operation 9.4.24. Killed 10.12.24. Exposure of the left vagus, which was under-ran by a skin-flap only.*

Post mortem. Nodular thickening in the first part of the aorta near the innominate artery.

Histology. Haemalum and eosin section. There was a proliferation of the intima, but no signs of necrotic changes. In the media the muscle-cells were obviously degenerating, and necrotic areas were in evidence.

Orcein section. Proliferation of elastic tissue in the intima and media with degeneration and fragmentation of the fibres.

8. *Rabbit. Ref. No. 953. Operation 18.6.24. Killed 10.12.24. Exposure of the left vagus, which was surrounded by a tubular skin-flap.*

Post mortem. Atheromatous plaques in the first part of the aorta.

Histology. Haemalum and eosin section. There was a diffuse intimal hyperplasia, and also a hypertrophy of the media. The muscle-cells appeared to be

undergoing changes, staining irregularly, swollen and irregular in outline, whilst the nuclei of these cells also presented a swollen appearance.

Orcein section. There was a definite proliferation of the elastica in the intima and subintimal layers.

Sudan III section. There is no fatty change.

9. *Rabbit. Ref. No. 954.* Operation 30.4.24. Killed 10.12.24. Exposure of right and left vagi, which were embedded in tubular skin-flaps.

Post mortem. Areas of whitish discoloration in the intima scattered about the arch of the aorta.

Histology. Haemalum and eosin section. There was proliferation of the intima, which occurred in the form of low raised patches or diffusely; the deep layers of the newly formed tissue showed foci of degeneration. There was no very definite medial change, but the smooth muscle-cells did not appear normal in parts.

Orcein section. There was a very decided increase of elastic tissue in the intima, and many of the larger fibres in the coinciding portions of the media showed fragmentation.

Sudan III section. There was a very marked fatty degeneration of the deeper layers of the intimal plaque and infiltration of the non-necrotic superficial cells.

10. *Rabbit. Ref. No. 955.* Operated 25.6.24. Killed 10.12.24. Exposure of the left vagus, which was surrounded by a detached muscle-flap.

Post mortem. Atheromatous nodules in the first part of the aorta.

Histology. Haemalum and eosin section. There was an increase of connective tissue in the intima, while the muscle-cells of the media showed signs of degeneration and separation. The outer layers of the latter coat were not affected.

Orcein section. There was a proliferation of elastic tissue in the intima and media corresponding to the thickened areas. The new elastic appeared to be showing early degenerative changes manifested by the fragmentation of the fibres.

The foregoing results show that ten of the cases subjected to exposure of the vagus presented pathological changes in the aorta. In seven there were definite nodular or plaque-like thickenings projecting into the lumen of the vessel, whilst in two there was present a whitish discoloration of the intima, slightly raised in one case, which corresponded to the microscopical changes, the one exception showing no macroscopical change being the first (No. 879). In the cases showing naked-eye lesions, the latter were most advanced in the first part or the commencement of the second part of the arch of the aorta, especially near the aortic valves or close to the origin of the innominate artery. In a few instances minor changes could be observed as far down as the origin of the upper intercostal vessels, but these were exceptional.

Coming to the histological appearances, firstly with respect to the intima, the sections stained with haemalum and eosin and orcein showed that in every case there were proliferative changes in this zone. This hyperplasia involves the endothelium, the areolar connective tissue, and the elastica. It is difficult to decide, especially in the early stages, whether the cellular increase is principally of endothelial or connective tissue origin, but, as far as can be judged, the principal factor is the latter: certainly in the later stages the proliferated connective tissue far exceeds any endothelial hyperplasia. As for the elastica,

the eight cases in which sections were stained with orcein all showed very decided intimal increase of this tissue except in animal No. 946, where in the section examined this change had occurred only to a minor degree. In four cases, or 40 per cent., there were signs of degeneration in this newly formed tissue as evidenced by the fragmentation of the fibres and small areas imperfectly stained with the orcein. In one instance a number of dark pigment granules appeared amongst the endothelial cells.

Out of the eight sections stained with Sudan III only two demonstrated the presence of fats; both had survived operation for a considerable time, undergoing the operation the same day, April 30, the first being killed on November 13, and the other on December 12. In the case of No. 946 the fat was present and fine globules in the wandering connective tissue cells of the intima, the section being taken near a plaque, whereas, in the other instance, passing through the centre of an intimal nodule there was advanced fatty degeneration, especially in the deepest layer of the proliferated zone, and a pronounced infiltration of fat between the layers of cells nearer the lumen of the vessel, which had not yet undergone necrosis. These results compare with those obtained by other investigators on the adrenalin arteriosclerosis, where, despite advanced intimal hyperplasia, fatty changes were infrequent, although calcareous infiltration was frequently noted.

Secondly, with respect to the media, the changes in the coat were not nearly so definite or as advanced as those in the inner layer. In every experiment there were signs of pathological change in the media, but in only two did this occur to any definite degree. Amongst these minor changes were localized hyperplasia corresponding to intimal thickenings, and staining variations of the muscle-cells, accompanied by separation of the medial elements, appeared to indicate early degeneration. These conditions were usually accompanied by slight elastic hyperplasia or fragmentation of this tissue at the foci of degeneration. In the experiments where the media showed more pronounced lesions these consisted of a definite proliferation and fragmentation of the elastic tissue, swelling of the muscle-cell nuclei, and inequality of staining accompanied by disappearance and separation of the smooth muscle-fibres. In no case was any fatty change discovered in this zone. Lastly, it may be noted that the recovery of these animals was remarkably rapid: within a few hours they appeared normal.

The Results of Sympathetic Irritation.

1. *Rabbit. Ref. No. 947. Operation 31.7.24. Died 7.11.24.* Exposure of the right and left superior cardiac sympathetic nerves; both were embedded in detached pieces of infrahyoid muscle.

Post mortem. Several small plaques in the first part of the aorta near the innominate artery.

Histology. Haemalum and eosin section. There was a diffuse proliferation of connective tissue in the intima. The media showed no specific change.

Orcein section. There was a marked increase of elastic tissue in the intima and innermost layers of the media, which was more pronounced at some points than others. At such points there was definite fragmentation of the fibres.

Sudan III section. A number of very small fat globules appeared in cells amongst the intimal interstices.

2. *Rabbit. Ref. No. 956.* Operation 31.7.24. Killed 10.12.24. Exposure of the left superior cardiac sympathetic branch, which was surrounded by a tubular skin-flap.

Post mortem. The first part of the aorta was very much dilated as compared with the transverse or descending portion; this was particularly so just above the aortic valves. On opening the vessel the latter region was covered with atheromatous ulceration and nodules. The plaques extended into the transverse part of the arch, but faded away in the descending portion, only one or two very small nodules thickening being found in the upper part of the thoracic aorta.

Histology. Haemalum and eosin section cut through a position of the transverse aorta not showing microscopical change. There was a proliferation of the intima; the media showed no definite lesion.

Orcein section through the same region. There was a proliferation of elastic tissue in the intima.

Sudan III section through the ulcerated area of the first part of the vessel. Very considerable intimal hyperplasia with secondary degeneration. The latter consisted of a marked deposition of fat and infiltration of calcareous salts. In some places these atheromatous abscesses had almost perforated the media or the intima. The muscle-cells of the media had undergone focal necrosis, and there was some fatty change.

3. *Rabbit. Ref. No. 957.* Operation 31.7.24. Killed 10.12.24. Exposure of the left superior cardiac sympathetic nerve, which was embedded in muscle and surrounded by a skin-flap.

Post mortem. Several plaques near the origin of the innominate artery, and a few very small ones around the orifices of the upper intercostal arteries.

Histology. Haemalum and eosin section not through a plaque. No very distinctive change; possibly a slight medial thickening.

Orcein section through same area. Some fragmentation of the elastic fibres of the intima, but nothing very obvious.

Sudan III section through a plaque area. Marked hyperplasia of the intima and media with fatty deposition throughout the intima, but occurring in larger masses at points.

4. *Rabbit. Ref. No. 959.* Operation 25.6.24. Killed 10.12.24. Exposure of the left superior cardiac cervical sympathetic nerve, which was surrounded by a skin-flap.

Post mortem. Plaques situated near the origin of the innominate artery and again after attachment of the aortic valve cusps.

Histology. Haemalum and eosin through the cusp nodules. There was a very definite hyperplasia of connective tissue in the intima, which was especially marked at the cusp attachment. This proliferation extended deeply into the media and the newly formed tissue appeared to be undergoing a hyaline change. In one plaque this tissue appeared not to have advanced as far as in the other node, the cells and their nuclei being more distinct and rounder, whereas in the other the nuclei appeared compressed between the fibrous trabeculae.

Orcein section of the same area. At the nodes there was a marked hyperplasia of the elastica around their bases, this tissue fading away towards the focus of degeneration. There was also a subintimal proliferation of elastic tissue, and again in the outer layers of the media.

Sudan III section. There was a fatty infiltration of the intima.

The results of sympathetic irritation show a fairly constant series of aortic changes. Firstly, with respect to the macroscopical lesions, it will be noted that in all four positive cases there were nodular thickenings in the first part of the aortic arch, and in all cases these were represented in the region of the origin of the innominate artery, even in the case which showed thickenings near the aortic valve cusps. The frequency of these lesions near the innominate is quite a striking feature.

Secondly, with respect to the histological changes, these likewise have progressed in each instance to a similar degree—that is, through the stages of intimal and medial hyperplasia to secondary degeneration in the deeper parts of the newly formed tissue of the former.

Thirdly, as regards the post-operative survival period, the average interval was $133\frac{1}{2}$ days, and in two cases, Nos. 956 and 957, 132 days. In comparison with these figures the survival period of the one negative experiment was 60 days, the animal dying of pleurisy. Finally, it may be recorded that two of the animals subjected to this operative interference with the cervical cardiac sympathetic showed a dilated pupil on the operated side, in the other no appreciable change was seen.

The Results of Depressor Irritation.

1. *Rabbit. Ref. No. 948.* Operation 28.8.24. Killed 21.11.24. Exposure of the depressor nerve, which was under-ran by a skin-flap.

Post mortem. Faintly defined areas in the first part of the aorta slightly elevated above the surrounding intima.

Histology. Haemalum and eosin section. Slight diffuse intimal hyperplasia. The media showed degenerative changes in the smooth muscle-fibres and also necrotic foci.

Orcein section. There were areas of proliferation of elastic tissue in the intima.

Sudan III section. There was an early fatty infiltration of the intima, the fat globules being contained by wandering connective tissue cells in the intimal interstices.

2. *Rabbit. Ref. No. 960.* Operation 28.8.24. Killed 10.12.24. The depressor nerve was under-ran by a skin-flap.

Post mortem. Plaque formation near the base of the aorta and a well-defined ulcer situated in this area. The aortic wall was almost perforated.

Histology. Haemalum and eosin section. Lateral to the ulcer there was a marked proliferation of the intima, increasing in depth until it culminated in a conical plaque. Both endothelium and connective tissue appeared to participate in this hyperplasia. The muscle-cells of the media showed degenerative changes, the nuclei irregularly stained and swollen. At the site of the ulcer the entire intima and two-thirds of the media had sloughed away. The remaining tissue showed impregnation, with calcareous particularly.

Orcein section. There was a proliferation of elastic tissue in the intima and subintimal zones, especially at the plaque. The media showed fragmentation of these fibres, which became widely separated and more broken up in the base of the ulcer.

Sudan III section. There was a fatty infiltration of the intima, but not in any advanced degree.

The positive results of depressor irritation again show changes in the first part of the aorta as in the preceding experiments. The lesions themselves present much the same changes as in the other cases, the early intimal hyperplasia being accompanied by medial degenerations and followed by fatty infiltration of the intima and necrosis of the proliferated tissue. The case of ulceration, No. 960, was evidently the result of the rupture of an atheromatous abscess, such as was found in No. 956. The animals were remarkably sensitive to operative manipulations on the depressor nerve, which had to be executed with the greatest caution. Their post-operative recovery was very slow compared to the others, the rabbits being weak and lethargic for several days.

Controls.

It is generally admitted that rabbits are liable to arterial lesions; hence, in basing any conclusions on the results of experimental production of arterial disease, it is necessary to carefully control the results. It will be seen from the preceding work that in 90 per cent. of twenty positive experiments, including both electrical and operative methods of irritation, there were naked-eye lesions in the aorta, more particularly in the first part of that vessel. The aorta was, therefore, examined in a number of animals that had been subjected to confinement under similar conditions and had been operated on under general anaesthesia. The latter point is emphasized in view of a possible degenerative change consequent on the anaesthetic; all the animals were selected at random. Fourteen of them had undergone a rhizotomy involving from one to six spinal roots, generally of the posterior series, but in one or two cases of the anterior roots; the anaesthetic in each case was ether. Post-mortem examination showed no naked-eye lesions in the aorta in any case; in two there was noticeable a very marked accumulation of subpericardial fat, but no other change.

In a fifteenth animal, which had had the spinal cord divided in the lumbar region, there was likewise no gross pathological change.

Two animals which died on the table during an attempt to expose the depressor nerve showed no macroscopical change in the aorta.

Lastly, no lesions in this region were found in four animals that had undergone operation on the external popliteal nerve and which had died a day or so later due to pleurisy.

In one rabbit which had been killed for dissection, and had not been operated on, there was a small plaque in the first part of the aorta. The animal was old, had been in the cage for a considerable time, and was blind in both eyes.

This is the only instance out of twenty-two consecutive cases where there was a naked-eye lesion due to the so-called idiopathic arteriosclerosis of rabbits, that is, in 4.5 per cent., whereas 90 per cent. of twenty positive experimental animals presented such lesions.

Coming to the question of microscopical changes, the results are controlled

on this side by the experimental negatives and special control animal. The latter had been subjected to confinement as in the experimental cases. No microscopical lesions were found in the aorta. Out of the four adrenalin cases, three presented no aortic changes that could be found by either microscopical or post-mortem investigation. The evidence of these is especially valuable, in view not only of their confinement, but from the fact that they had been subjected to the administration of a recognized arterial irritant, adrenalin, over a period which usually excites pathological changes in the aorta.

Finally, in three of the vagal experiments, one sympathetic and one depressor, there were negative results, whilst one vagal result is discarded on account of the death of the animal, shortly after operation, from acute serofibrinous pleurisy; there were no aortic lesions. This gave us a total of ten cases showing no naked-eye or microscopical changes out of a series of thirty-nine animals, from which it is inferred that the relative incidence of idiopathic arterial disease in rabbits is not of such frequency as to jeopardize any conclusions based on the experiments.

Conclusions.

The results of experimental inquiry in the aetiological relations between the aorta and its nerve-supply have shown :

1. In ten out of a series of thirteen rabbits (exclusive of fallacies) subjected to operative irritation of the vagi there is endarteritis of the aorta, more particularly of the first part of the aortic arch.
2. Four out of a series of five animals subjected to operative irritation of the cervical sympathetic present similar lesions.
3. Two out of a series of five animals subjected to operative irritation of the depressor nerve also showed endarteritic lesions in the aorta, but it must be remembered that two others succumbed during operation.
4. All three cases subjected to electrical stimulation presented these lesions.
5. That after due allowance is made for idiopathic lesions there still remains a major percentage of cases which must be accounted for by the nerve irritation.
6. The constancy of the naked-eye lesions in the vicinity of the origin of the innominate artery or at the base of the aortic arch and the absence of similar lesions lower down that vessel are urged as evidence favouring a neurological origin of the same.
7. That the pathological changes are constant ones and progress through a definite sequence, the earliest consisting in a proliferation of the intima in which both endothelium and areolar and elastic tissues participate. This is followed by hyperplasia of the elastic fibres in the media and early signs of degeneration in the smooth muscle-cells. Fat is deposited in the intima, and the deeper layers of this zone undergo necrosis, with the formation in advanced cases of atheromatous abscesses, sloughing of the inner layer of the intima, and the formation of ulcers.

It is not the purpose of the present paper to discuss the clinical application of these results, but it may be indicated here that they have a considerable bearing on the question of aortic disease associated with nervous phenomena; for example, such as occur in angina pectoris. The question of a primary nerve lesion with secondary vascular changes being raised, this subject is discussed elsewhere.

Lastly, I tender my sincere thanks to the Committee for the Tom Jones Memorial Surgical Fellowship for permission to publish these results; to Professor J. S. B. Stopford for kindly reading the type-script; and to Professor Raper and Dr. McSwiney for permission to carry out the experimental work in the Physiological Department of the Victoria University and for facilitating the research in many ways.

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TABLE I

Analysis of General Results.

General Data.	Method of Nerve Irritation.					
	Opera- tive on the Vagus.	Opera- tive on the Sym- pathetic.	Opera- tive on the De- pressor.	Electrical.	Adrenalin.	Electrical and Adrenalin.
Total number of ex- periments	22	5	5	3	4	1
Number of survivals	18	5	3	3	4	1
Approximate opera- tive mortality	18.1 %	—	40 %	—	—	—
Number of positive results	10	4	2	3	1	1
Number of negative results	3	1	1	0	3	0
Number of results dis- carded due to inter- current disease	5	—	—	—	—	—
Average post-opera- tive survival period in days	133.8	132.5	95.0	125.3	79.0	266

TABLE II

Analysis of Positive Cases.

	Experimental Methods of Nerve Irritation.							
	Irrita- tion of Left Vagus.	Irrita- tion of both Vagi.	Irrita- tion of Left Sym- pathetic.	Irrita- tion of Left and Right Sym- pathetic.	Irrita- tion of the De- pressor.	Elec- trical Irrita- tion.	Adre- nalin Irrita- tion.	Elec- trical and Ad- renalin Irrita- tion.
Number of posi- tive cases in each heading	9	1	3	1	2	3	1	1
<i>Nature of Lesions:</i>								
Early prolifera- tion of the in- tima	+(1)	—	—	—	—	+(2)	+(1)	—
Early change in the media	+(7)	+(1)	—	—	—	+(2)	+(1)	—
Advanced hyper- plasia of the in- tima	+(8)	+(1)	+(3)	+(1)	+(2)	+(1)	—	+(1)
Advanced degen- eration of the media	+(2)	—	+(3)	—	+(2)	+(1)	—	+(1)
Proliferation and fragmentation of the elastic tissue	+(8)	+(1)	+(3)	+(1)	+(2)	+(1)	—	+(1)
Fat in the intima	+(2)	+(1)	+(3)	+(1)	+(2)	+(1)	—	+(1)
Abscess or ulcer	—	—	+(1)	—	+(1)	—	—	—
Plaque formation	—	—	+(3)	+(1)	+(2)	+(1)	—	+(1)

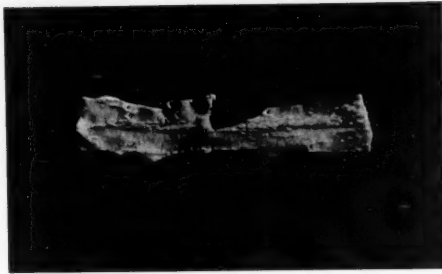


FIG. 1. Aorta. Advanced atheroma, showing linear distribution of plaques.



FIG. 2. Ascending aorta. Small plaque on left side of innominate artery.



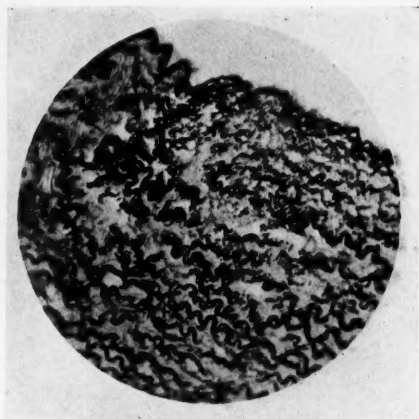


FIG. 3. Fragmentation of elastic fibres in the intima and media.

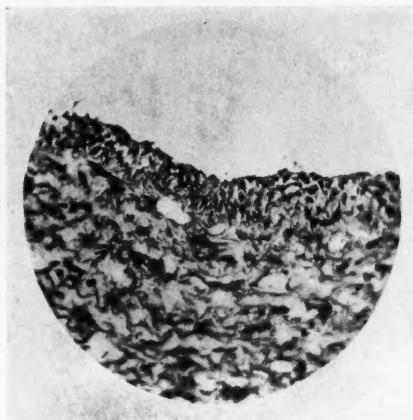


FIG. 4. Early proliferation of the intima. Degeneration of smooth muscle cells in the media.

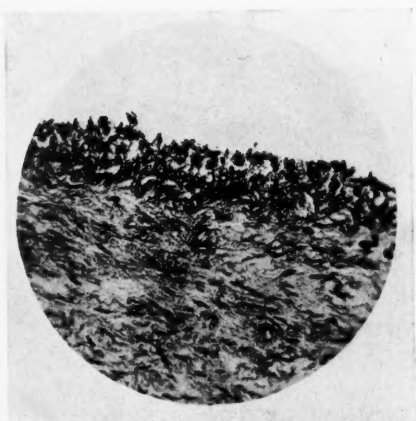


FIG. 5. Early proliferation of the intima.

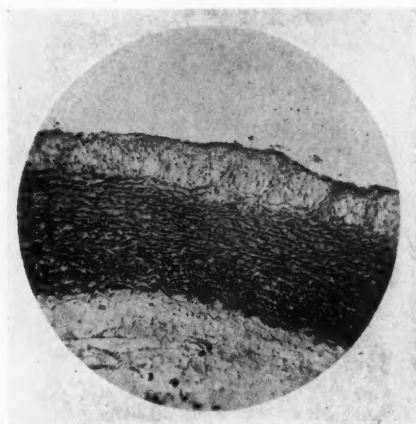


FIG. 6. Intimal hypertrophy with degeneration in the deeper layers.

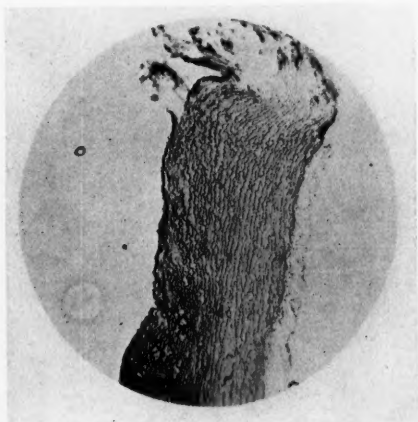


FIG. 7. Bottom: intimal plaque. Proliferation of elastica. Top: atheromatous ulcer. Degeneration of elastica.

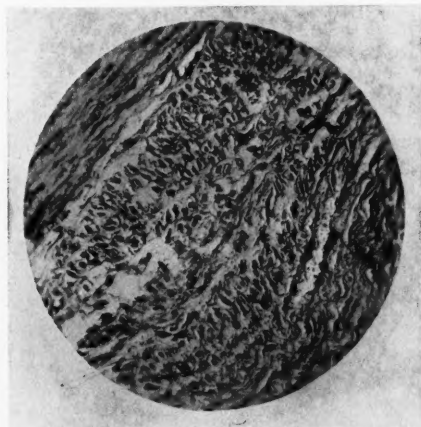


FIG. 8. Degeneration of muscle cells in the media. Proliferation of connective tissue.



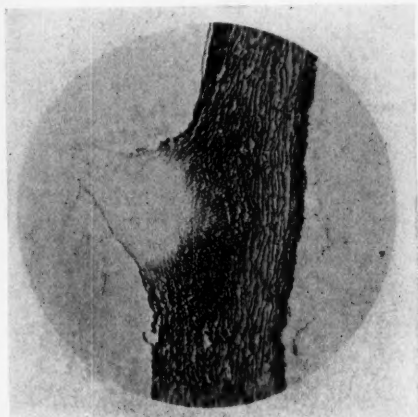


FIG. 9. Atheromatous plaque. Hyperplasia of the elastic tissue.

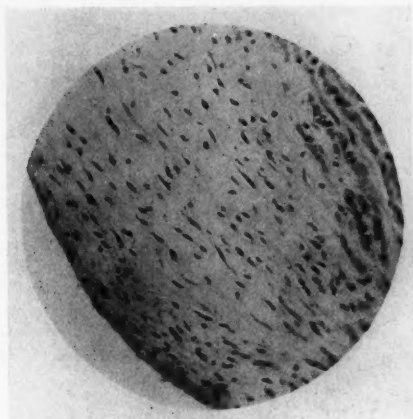


FIG. 10. Hyaline degeneration of fibrous tissue in an intimal plaque.



FIG. 11. Atheromatous ulcer. Intima and part of the media have sloughed.

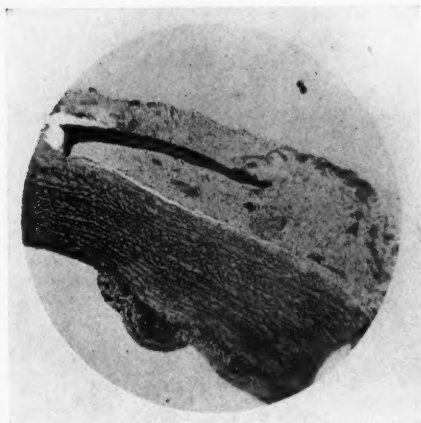


FIG. 12. Fatty degeneration in an intimal plaque.

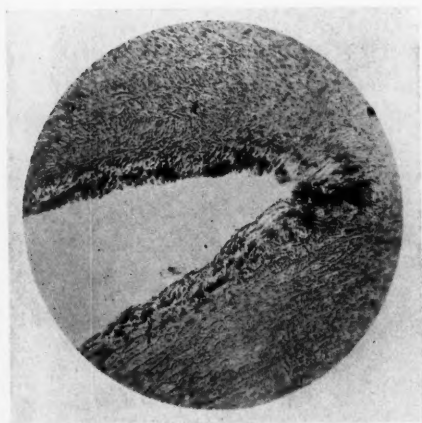


FIG. 13. Hyperplasia of the intima and fatty degeneration.

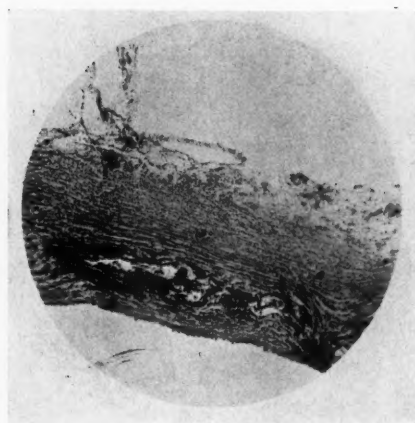


FIG. 14. Atheromatous abscess in hypertrophied intima.



CAN INSULIN PRODUCE EVEN A PARTIAL CURE IN HUMAN DIABETES MELLITUS?¹

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Introduction

MUCH has been written in the lay press about the 'cure' of diabetes with insulin, and many are the occasions on which a medical man has had to disillusion some unfortunate sufferer. To the writer's knowledge no case of diabetes mellitus has yet been published in which it was possible eventually to stop the insulin entirely and to allow an absolutely unrestricted diet, without the return of hyperglycaemia. Whilst then the possibility of a complete cure is apparently out of the question, it is not without interest and importance to try to decide whether even a partial cure can be ascribed to the action of insulin.

Method of Investigation.

The patients were placed on a constant daily intake of carbohydrate, protein, fat, and calories, and the dose of insulin was adjusted to keep the blood-sugar within normal limits.

The observations reported later in this paper were made on five patients who had been the subjects of a number of previous investigations on insulin treatment. It was only necessary, therefore, to fix the intake of food rigidly, to adjust accurately the dose of insulin, and thereafter to examine the patients at intervals to demonstrate that the level of blood-sugar was satisfactorily under control. The observations on these five cases provide data as to whether or not insulin can cause a remission of the disease when treatment is prolonged over many weeks. In other words, an attempt has been made to obtain indirect evidence which might reasonably be interpreted for or against the formation of fresh islet cells.

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² Working on diabetes with a grant from the Medical Research Council.

(Q. J. M., Jan., 1926.)

The estimations of sugar in the blood have been made by Cole's (1) or by MacLean's (5) method, the former for the first four years, the latter for the last fifteen months. In the writer's hands Cole's has yielded consistently slightly lower values than MacLean's method.

Benedict's quantitative and qualitative methods have been used for sugar, Gerhardt's ferric chloride test for diacetic acid, and Rothera's nitroprusside test for acetone and diacetic acid in the urine. The limit of sensitivity of Gerhardt's test is about 1 in 14,000, and of Rothera's test about 1 in 20,000 for acetone, and about 1 in 400,000 for diacetic acid (2).

The diet calculations have been based on the average values collected in a book by Dr. R. D. Lawrence and the writer (3). In calculating the caloric values of the diet no allowance has been made for loss in the faeces, i. e. the calories as calculated are 'calories gross'. Calculations have been made on the usual basis, viz. that 1 gm. carbohydrate yields 4.1, 1 gm. protein 4.1, and 1 gm. fat 9.3 calories. The glucose equivalent (7) of the diet has been computed from the formula $G = C + 0.58P + 0.1F$, i. e. on the assumption that in metabolism 1 gm. carbohydrate yields 1 gm., 1 gm. protein 0.58 gm., and 1 gm. fat 0.1 gm. glucose. The patients were weighed without clothes to the nearest ounce; the weight has been recorded to the nearest pound in the tables. When the weight had to be measured with clothes, these clothes were subsequently weighed separately and due allowance made. If this was not possible, 10 lb. were allowed for clothes in the case of the male and 6 lb. in the case of the female (4).

For insulin injections 1 c.c. syringes, calibrated in twentieths or hundredths of a c.c., were used. The dose is recorded throughout as so many clinical units.

Results.

Five patients have been kept under observation for periods of 46 to 83 weeks, each on a fixed daily intake of carbohydrate, protein, fat, and calories. The results are recorded in tabular form (Tables I, II, and III). All five had been under observation for long periods beforehand, and a number of investigations on dietetic and insulin treatment had been made. The diet of each was then fixed and the insulin dosage adjusted thereto. It is with this last period only that we are here concerned. A few notes in explanation of the variations in insulin dosage are necessary.

Case 7. This is the only case in which it ever looked as though some real improvement in the diabetic state had occurred. It shows well how essential it is to draw no conclusions from observations lasting for only 10 to 20 weeks. Reviewing the result now, some six months after the completion of the observation, I would ascribe the *apparent* improvement to two things: (a) the difficulty of balancing the dose of insulin against the diet, and (b) variations in the strength of different batches of insulin. The initial dose of 30 units daily was a little too high. To avoid hypoglycaemic reactions the dose was reduced,

but the reduction was larger than it should have been. The rise to 35 units in my opinion was necessitated by a falling off in the strength of the insulin. Five of my patients all relapsed at this same time, and had to have the dose of insulin increased. Subsequently all five went back to their previous dose when a satisfactory batch of insulin was substituted.

Case 8 needed at least as much insulin at the end as at the beginning of the period of observation. In fact the figures suggest that he needed more at the end. Though his total body-weight had not increased, one feels that his 'metabolically active' tissue must have increased. His muscles were firmer and he was much stronger. This in itself might necessitate a slight increase of insulin. There was obvious though slight oedema at the beginning of the period. Water retention slowly gave place to storage of fat and gradual increase of muscle. Hence the body-weights are misleading. The variations in insulin dosage are partly accounted for by variations in the strength of different batches.

Cases 14, 42, and 66 all put on weight and all required as much or more insulin at the finish as at the start.

Table III shows the blood-sugar curves made periodically in one of the five cases in order to control the dose of insulin. The remarks at the bottom of each curve indicate the directions given on the next day as the result of that particular curve. The table is constructed from the observations on *Case 42*. It is typical of the results obtained in each of the five cases. Altogether about 800 estimations of blood-sugar were made on these five patients during the period under review. In each instance the estimations were made in duplicate and the mean recorded.

The conclusion to be drawn from these prolonged observations is, I think, obvious. Insulin does not produce even a partial remission of the disease in the adult. To put the matter another way, for a given load of food there is no evidence at the end of twelve months and more that the 'extra horse-power' required in the shape of exogenous insulin is any less.

At the same time insulin seems to have arrested the downward progress of the five patients, and that is saying a very great deal. All five were becoming steadily worse until insulin was started. It is very doubtful whether four of them would have been alive now without insulin. It is true that the diets used in the pre-insulin periods were not the best from the modern point of view (except in *Case 66*). It is therefore not fair to ascribe the cessation of the downward progress entirely to the insulin. But, quite apart from that, the fact remains that over the periods covered by Table II there has been no downward progress if a slight increase in dosage be allowed for increase of tissue. It is concluded, then, that although these five patients are no less dependent on insulin, they are also not more dependent on it. Judging from these observations, the diabetes has been arrested, but not in any sense cured.

TABLE I.

Case No.	Sex.	Age.	Fixed Diet.			Glucose equiva- lent. Grm.	Calories per diem.	Calories per kg.	Total Weeks on Fixed Diet.
			C.	P.	F.				
7	F.	34	40	60	140	89	1710	42	46
8	M.	32	45	80	140	105	1810	28	64
14	M.	36	20	70	120	73	1490	23	83
42	F.	32	20	60	120	67	1450	25	77
66	M.	47	35	70	120	88	1550	25	61

TABLE II.

Period of Observation.	No. of Weeks.	Insulin per diem. Clinical units.	Range of Glycaemia. Mg. per 100 c.c.	Body-weight without Clothes.	
				Lb.	Kg.
Case No. 7.					
31.11.23- 7.12.23	1	30	60-120	83	37.7
8.12.23-10.12.23	$\frac{1}{2}$	24	60-140	84	38.1
11.12.23-14.12.23	$\frac{1}{2}$	19	80-160	84	38.1
15.12.23- 1. 1.24	$2\frac{1}{2}$	16	90-180	86	39.0
2. 1.24- 8. 4.24	14	14	100-270	87	39.5
9. 4.24-17. 4.24	1	25	140-230	87	39.5
18. 4.24-15. 5.24	4	30	120-200	88	39.9
16. 5.24-27. 5.24	2	35	90-180	88	39.9
28. 5.24-16.10.24	$20\frac{1}{2}$	25	70-170	90	40.8
Case No. 8.					
15.12.23-24.3.24	$14\frac{1}{2}$	16	90-190	145	65.8
25. 3.24- 5.4.24	$1\frac{1}{2}$	24	100-200	144	65.3
6. 4.24- 3.6.24	$8\frac{1}{2}$	30	90-180	142	64.4
4. 6.24-18.7.24	$6\frac{1}{2}$	22	90-230	143	64.8
19. 7.24- 7.9.24	$7\frac{1}{2}$	30	90-190	144	65.3
8. 9.24-27.1.25	20	32	70-180	149	67.7
28. 1.25- 9.3.25	6	30	80-160	144	65.3
Case No. 14.					
5. 8.23-19. 8.23	2	45	90-350	118	53.6
20. 8.23-26. 8.23	1	40	70-230	122	55.3
27. 8.23-14. 9.23	$2\frac{1}{2}$	36	70-200	124	56.3
15. 9.23-29.10.23	$6\frac{1}{2}$	30	70-300	131	59.4
30.10.23- 9. 3.25	71	40	60-270	144	65.3
Case No. 42.					
5.8.23-25.9.23	7	30	70-210	113	51.3
26.9.23- 9.1.24	15	35	100-190	122	55.3
10.1.24-17.2.24	5	31	90-200	122	55.3
18.2.24-11.4.24	8	40	100-240	123	55.8
12.4.24-17.5.24	5	46	100-170	124	56.3
18.5.24-29.7.24	10	30	90-160	125	56.7
30.7.24-14.9.24	$6\frac{1}{2}$	34	90-140	127	57.6
15.9.24- 7.2.25	21	40	80-160	129	58.6
Case No. 66.					
5.1.24-15.1.24	$1\frac{1}{2}$	10	130-210	124	56.3
16.1.24-25.1.24	1	12	160-220	128	58.1
26.1.24-17.4.24	12	14	140-270	133	60.3
18.4.24-12.6.24	8	20	60-130	136	61.7
13.6.24-18.9.24	14	18	60-210	142	64.4
19.9.24- 9.3.25	$24\frac{1}{2}$	20	60-270	144	65.3

TABLE III.

No. of weeks on fixed diet	1	1½	3½	5	7	8	10	13½	18	22	24	27	35	39	40	44½	50	56½	69½	77	
Morning dose of insulin	20	20	20	20	20	20	20	20	20	20	18	18	20	23	23	15	15	17	20	20	
Hours after insulin	0	1	1½	2	3	4	4½	5	6	7½	24	Blood-sugar, mg. per 100 c.c.									
	191	162	157	155	183	178	160	180	146	107	162	220	224	96	100	157	190	142	114	150	
	173	145	107	143	179	—	147	164	183	142	—	—	241	123	—	155	—	132	—	172	
	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	162	—	
	104	110	70	92	149	—	109	112	146	142	—	—	218	135	—	104	—	117	114	112	
	—	—	—	—	—	—	—	—	—	—	—	—	—	134	—	—	—	92	130	130	
	116	125	112	132	128	—	122	112	123	113	—	—	175	—	—	90	—	100	105	108	
	—	—	—	—	—	—	—	113	—	—	—	—	—	180	—	—	—	103	—	102	
	142	144	131	137	118	—	142	119	117	105	—	—	216	119	—	110	—	192	88	100	
	162	162	159	—	159	—	160	125	120	—	—	—	—	—	—	—	—	159	—	—	
	190	—	—	—	200	—	—	155	150	106	—	230	—	—	—	—	—	—	122	—	
Evening dose	10	10	10	10	10	15	15	15	15	15	13	13	20	23	23	15	15	17	20	20	
Total insulin in 24 hours	30	30	30	30	30	35	35	35	35	35	31	31	40	46	46	30	30	34	40	40	
Remarks	Continue 30 units	Continue 30 units	Continue 30 units	Continue 30 units	Continue 35 units	Continue 35 units	Continue 35 units	Continue 35 units	Continue 35 units	Continue 35 units	Continue 31 units	Continue 40 units	Ordered 46 units	Continue 46 units	Ordered 30 units of different make of insulin	Continue 30 units	Ordered 34 units	Ordered 40 units of another brand of insulin	Continue 40 units	Continue 40 units	

Note.—Breakfast ½ hour and dinner usually 3½ hours, but sometimes 3 hours, after the first dose of insulin. Second dose usually 7½ hours after the first dose of insulin, followed in 15 to 30 minutes by tea, and in 3 to 3½ hours by supper. Sometimes the second dose of insulin was taken 9 hours after the first, and ½ hour before supper. The blood-sugar at the end of 24 hours of course is the fasting level before insulin on the following day.

Difficulties of Investigation.

Throughout such an investigation as the present one, naturally the improvement of the patient's condition demands first attention. As a result, it has not been possible so far to make observations on any one fixed diet for a period of more than eighteen months.

Secondly, a given observation may be spoilt by the onset of an intercurrent disease, which itself may necessitate a change of diet, or of the dosage of insulin, or of both. It is well known that almost any form of sepsis tends to aggravate the diabetic condition. If the diet remained fixed the dose of insulin would have to be increased when septic complications intervened. During the period of observation on the five cases reported in this paper, no serious infection occurred. All five had slight colds in the head on one or two occasions, but no alteration in diet or in the dose of insulin was necessary. In fact, all five were unusually well and strong throughout.

Thirdly, growth may be a complicating factor. Experience of diabetes in children is difficult to obtain, and therefore opinions must be expressed with greater caution. As a result of careful observations on a few suitable children, my present opinion is that the dose of insulin and the diet will have to be increased in proportion to one another to allow of satisfactory growth. If this is confirmed, the insulin treatment of children will indeed be complicated and laborious. It is already difficult enough, owing to the great problem of preventing diabetic children from breaking diet, and to their liability to intercurrent diseases.

This complication of tissue increase is not without importance also in the adult diabetic. Some diabetic patients put on as much as two stones in weight and more. No doubt much of this increase is often due to water retention, but many patients certainly lay down quantities of subcutaneous fat, and one's impression is that there is an actual increase in actively functioning tissue such as muscle. If this impression be an accurate one, then it would not be unreasonable to ascribe a slight increase in insulin requirements (on a fixed diet) to the extra metabolism of new tissue.

Fourthly, the quantity of exercise taken on a given day has a very real influence on the quantity of insulin required for that day. One of my patients on a fixed diet and a fixed dose of insulin always developed hypoglycaemic symptoms when he played strenuous tennis, and not otherwise. The influence of exercise is not important in observations extending over many months if the daily routine is kept reasonably steady. It is of course important to make certain that the 'test days', the days on which blood-sugar curves are made, are average days, and representative of the rest of the period of observation.

Lastly, a very real complication in my experience is variation in the strength of different batches of insulin. Using the same batch of insulin, on a fixed diet, with the patient's daily routine kept as regular as possible, the blood-sugar curve remains remarkably steady (Table IV). Every now and then,

on changing over to a new batch of insulin, a patient suddenly appears to relapse, or on the other hand suddenly develops hypoglycaemic symptoms. Simultaneously the blood-sugar curve rises or falls. Examples of comparisons between different batches of insulin are appended (Tables V and VI) to demonstrate these differences. It is recognized that every possible care and skill has been exercised to standardize insulin, and since the spring of 1925 successive batches have appeared to be of more uniform strength.

During the last six months (September 1924–February 1925) all my special patients have been on the same batch of insulin in order to avoid the above-mentioned difficulties. This has been a great boon both to the patients and myself, and was arranged through the courtesy of Messrs. The British Drug Houses, Ltd.

TABLE IV.

Case 42, showing Comparative Constancy of Blood-sugar Curves when all factors (intake of carbohydrate, protein, fat, times of meals, amount of exercise, amount of insulin) are kept constant.

Hours after Insulin.	Blood-sugar mg. per 100 c.c.		
	11.12.23.	12.12.23.	14.12.23.
0	146	150	158
$\frac{1}{2}$	177	158	157
$1\frac{1}{2}$	183	180	186
$2\frac{1}{2}$	166	164	154
$3\frac{1}{2}$	125	139	122
$4\frac{1}{2}$	123	124	122
$5\frac{1}{2}$	114	119	122
$6\frac{1}{2}$	120	111	121

TABLE V.

Comparison between two Batches of Insulin under Identical Conditions on Consecutive Days.

Hours after Insulin.	Batch A. 10 units.	Batch B. 20 units.
	Blood-sugar, mg. per 100 c.c.	
0	205	220
$1\frac{1}{2}$	164	223
$2\frac{1}{2}$	118	174
4	76	110

Note.—It will be seen from the above that 20 units of batch B were not so efficacious as 10 units of batch A. It is only fair to state that this comparison was made in early days (1923) before the methods of standardization were satisfactorily established. Batch A was made by a different firm from batch B. Such gross differences are probably never to be met with nowadays. Certainly two batches made by the same firm would never exhibit such wide differences now. At the same time variations of such a magnitude as to be troublesome in clinical work do still occur (Table VI).

TABLE VI.

Comparison between two Batches of Insulin issued by the same Firm in the last Six Months of 1924.

Hours after Insulin.	Batch E. 18 units.	Batch F. 18 units.
	Blood-sugar, mg. per 100 c.c.	
0	237	217
1	234	249
2	235	202
3	224	160
4	185	124
5	174	90
6	158	85

Breakfast 20 mins. after insulin of C = 15, P = 16, F = 44½.
Dinner 3 hrs. 20 mins. after insulin of C = 15, P = 23½, F = 34½.

The two curves were obtained under identical conditions on consecutive days. Batch F is obviously stronger than batch E.

Variations in the Dose in the First Few Days of Insulin Treatment on a Fixed Diet.

In common with many other workers, I have often found it necessary to reduce the dose of insulin during the first few days of insulin treatment, the diet being constant, in order to keep the blood-sugar at a steady level. Cases illustrating this are given below.

Does this initial reduction of dosage indicate any real improvement in the diabetic state? Arguing on the basis of Allen's work it is conceivable that during these first few days pancreatic islet-cells in a state of active degeneration may recover and add their quota of endogenous insulin. It is, however, at least equally possible that the reduction in dosage is simply the result of the action of the insulin on metabolism. When exogenous insulin is introduced in amounts sufficient to bring the blood-sugar down to 100 mg. per 100 c.c. or less for several hours from the very first day, a considerable disturbance of the previous metabolism is suddenly caused. It would be expected (with each change of insulin dosage, or of diet, or of both) that several days would be required in order to restore a new balance. It is essential to remember that the blood-sugar percentage is the resultant of a number of factors—the amount of glycogen stored, the quantity of insulin available, the call for sugar by the tissues, the food intake, &c., &c.—and we are able to measure quantitatively only a few of these factors. Though the possibility of some degree of recovery of degenerate islet-cells cannot be excluded, it would seem to me more satisfactory to regard the initial fluctuations of dosage as part of the establishment of a new 'metabolic balance'. Fuller consideration of this point is given in the discussion following the description of the cases below.

TABLE VII.

Days of insulin treatment	0	1	2	4	7	11	17
Dose of insulin, units	0	16	12	12	12	10	10
	Blood-sugar, mg. per 100 c.c.						
Before insulin	176	160	137	152	173	196	193
1½ hours after	166	94	100	114	102	128	157
3½ " "	166	90	81	89	79	96	95
5½ " "	160	85	104	91	96	108	114
6½ " "	161	74	114	94	104	128	129

Cases of Diabetes requiring Alterations in Dosage during the First Few Days of Insulin Treatment on a Fixed Diet.

Case 66. M., aged 45. Before insulin treatment was started the patient took daily 20 gm. carbohydrate, 60 gm. protein, and 90 gm. fat, which amounted to 24 calories per kg. On and after the first day of insulin administration the diet was fixed at 30 gm. carbohydrate, 70 gm. protein, and 110 gm. fat, or 28 calories per kg. Breakfast was given half an hour, and lunch three and a half hours, after the insulin, which was taken fasting in a single dose only. Breakfast contained 10 gm. carbohydrate, 29 gm. protein, and 46 gm. fat, whereas lunch amounted to 10 gm. carbohydrate, 22 gm. protein, and 29 gm. fat.

It will be noticed that the dose of insulin had to be reduced in eleven days from 16 to 10 units in order to keep the blood-sugar as nearly steady as possible. It is not without interest to speculate as to the meaning of the fluctuations in the blood-sugar.

Insulin in the diabetic not only helps to combust glucose, it also aids the storage of sugar as glycogen. Case 66 had been on a low diet for several weeks, on which it was possible to keep his blood-sugar between 150 and 180 mg. per 100 c.c., but he was steadily losing strength and weight. Presumably his glycogen stores were depleted when the first dose of insulin was given. As a result he would not have much glycogen to call upon as the insulin removed the sugar from the blood. Accordingly there was a prolonged fall of blood-sugar after the first dose and there were still no signs of its rising 6½ hours after the insulin. This idea is further borne out by the lower fasting level on the second day. The next point to note is the rise of the fasting level to 196 mg. on the eleventh day. This I would account for as follows: Under the action of insulin, glucose is stored as glycogen for the first few hours of each day. Later in the day the action of the insulin wears off, sugar is called for by the tissues, and as a result some of the sugar which was stored earlier in the day is now mobilized. But the tissues are now unable to utilize dextrose completely, and therefore the concentration of the latter in the blood tends to rise. Hence every day there is first of all a storage of sugar, and later a mobilization of that sugar. The fasting level tends to rise until a new balance is established, when it remains relatively steady under constant conditions for many weeks.

Of course in this case the patient's fasting hyperglycaemia could have been reduced by a second injection of insulin in the evening. In more severe cases,

however, it is difficult and sometimes impossible to bring the fasting level to within normal limits with two or even three daily doses of insulin.

Case 71. M., aged 45. This case is interesting in that the effect of a constant diet was demonstrated before adding insulin to that same diet. Unfortunately the patient later broke diet and therefore further observation would have been valueless. The fixed diet consisted of 36 gm. carbohydrate, 75 gm. protein, and 111 gm. fat daily, or 30 calories per kg. The results of diet alone are given in Table VIII.

TABLE VIII.

Day of Treatment.	Fasting Blood-sugar, mg. per 100 c.c.	24 hours' urine.	
		Glycosuria, gm. per diem.	Ketonuria (Rothera).
0	490	67.1	+++
2	205	51.8	+++
3	193	68.5	++
4	169	60.6	+++
6	177	54.4	++
9	185	27.7	++
13	180	11.7	+
16	180	9.7	trace
18	182	9.8	trace

On the nineteenth day insulin was started (Table IX):

TABLE IX.

Day of insulin treatment	1	2	3	4	6	7	8
Dose of insulin, units	10	8	5	0	5	5	5
Blood-sugar, mg. per 100 c.c.							
Before insulin	182	83	93	102	205	154	158
1½ hours after insulin	107	60*	94	—	146	—	—
3 " " "	95	50*	65*	—	113	85	117
4½ " " "	106	65*	67	—	88	—	—
6 " " "	78	80	67	—	110	89	—

* Hypoglycaemic symptoms.

Breakfast was given half an hour, and lunch 3 hours, after the insulin. As in the previous case (Case 66) the blood-sugar on the first day was still falling 6 hours after the insulin, but it was 99 mg. per 100 c.c. 7½ hours after the insulin (not recorded in the above table). It was therefore very surprising to find the fasting level only 83 on the second day, but it was not at all to be wondered at that the patient developed bad hypoglycaemic symptoms later in the day, for which 15 gm. sugar (in the form of orange-juice by mouth) had to be given. No insulin was given on the fourth and fifth days. The diet was kept constant throughout. As a result there was definite hyperglycaemia on the morning of the sixth day. Finally a satisfactory balance against a single dose of 5 units of insulin daily was established, and maintained for just over two weeks, when the patient decided to alter the diet (and later his insulin also!) according to his own liking, and was therefore discharged from hospital.

The dose of insulin on the first day (10 units) would appear to have been correct, the blood-sugar being 99 mg. per 100 c.c. 7½ hours after the insulin.

Supper (without further insulin) was given an hour and a half later, and therefore no alarm was felt during the night, and the patient had no hypoglycaemic symptoms.

On the second day the dose was too large. The injection was made before the first analysis was completed. The result of this analysis, however, gave us ample warning of what was to follow and therefore due preparation was made. The only suggestion that I have to make in explanation of the prolonged effect of insulin in the first 24 hours is that the patient's stores of glycogen must have been considerably depleted by the previous dietetic treatment without insulin. Perhaps, however, I did not persist long enough with dieting alone.

TABLE X.

Day of insulin treatment	0	1	2	4	8	11	17	31
First dose of insulin, units	0	14	10	12	12	15	14	14
	Blood-sugar, mg. per 100 c.c.							
Before insulin	256	245	264	270	238	172	249	222
2½ hours after insulin	279	89	149	161	183	69	217	66
3½ " " "	283	85	63	105	158	78	158	69
6½ " " "	—	103	186	155	119	99	138	85
Second dose of insulin, units	0	6	6	8	10	10	10	10
Total insulin per diem	0	20	16	20	22	25	24	24

Case 65. M., aged 11. Before the start of insulin treatment the patient's diet had been reduced to 25 grm. carbohydrate, 50 grm. protein, and 80 grm. fat for a week, on account of a bad relapse of his diabetes owing to 'influenza'. On and after the first day of insulin, the diet was fixed at 80 grm. carbohydrate, 60 grm. protein, and 160 grm. fat, or 62 calories per kg. Breakfast (C = 20, P = 15, F = 45) was given half an hour, and lunch (C = 25, P = 20, F = 40) 3½ hours, after the first dose of insulin. The second dose was given 6½ hours after the first, and was followed in 15 minutes by tea (C = 20, P = 15, F = 40) and in 3½ hours by supper (C = 15, P = 10, F = 35).

It will be noted that it was only necessary to reduce the dose of insulin a little on the second and third days. Thereafter the dose had to be increased slightly. Fasting hyperglycaemia was rather marked in spite of two doses of insulin daily. It will be noted that the blood-sugar tends to swing considerably from high to low and back again to high values. This patient developed no symptoms with blood-sugars of 60 mg. per 100 c.c.; in fact, on several occasions figures as low as 40 mg. were registered without hypoglycaemic symptoms. It is my experience that the level of blood-sugar at which symptoms occur is decidedly lower in children than in adults. This might be expected, since the general level of the blood-sugar of healthy children is set at a lower figure than that of adults (*vide* Spence (6)).

That the initial reduction in insulin on the second and third days was so small, and that subsequently a slight increase in dosage was called for, I attribute to the large diet with a relatively high proportion of carbohydrate. Likewise the swing to low and back to high values is the rule with large diets and large doses of insulin.

Summary.

1. As a result of observations lasting from eleven to eighteen months on five selected cases of diabetes mellitus, no evidence has been obtained of even a partial remission of the disease. The daily intake of carbohydrate, protein, fat, and calories remained fixed throughout. The dose of insulin was adjusted to the fixed diet according to the results of estimations of the blood-sugar content.

2. All five patients needed as much or slightly more insulin at the end of the observations.

3. Such fluctuations in dosage as occurred are considered to be due to (a) the difficulties in balancing the dose accurately against the diet, (b) variations in the strength of different batches of insulin from various sources, (c) increase in metabolically active tissue.

4. Various difficulties in such an investigation are noted and means of avoiding them are outlined.

5. Illustrations of the variations in the daily dose of insulin at the beginning of treatment on a fixed diet are given, and their significance is discussed.

Acknowledgements.

I owe whatever value there may be in this thesis to the loyal co-operation of the patients. They are not many in number, but have become personal friends, and have taken as keen an interest in the investigations as I have.

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Lastly, I desire to express my gratitude for a personal grant, and grants for expenses, to the Medical Research Council.

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PATHOLOGICAL VARIATIONS IN THE SERUM CALCIUM¹

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At the commencement of this work it was intended to determine the total calcium content of the serum in the commoner skin diseases, and to observe the effect, if any, of administration of calcium salts and of parathyroid. Soon, however, the scope of the investigation was extended to include other pathological conditions which were readily available. The chief reason determining this change was the fact that, most of the patients suffering from skin diseases being treated as out-patients, adequate supervision of diet, &c., was usually impossible.

Methods.

The method used for the estimation of calcium was that of Kramer and Tisdall (1), which had already been thoroughly tested by one of us and found to be sufficiently reliable. Duplicate determinations invariably agreed within 2-3 per cent., so that a variation of 10 per cent. in the serum calcium content (i. e. 1 mg. per 100 c.c.) may be considered as being undoubtedly real, while to variations of over 5 per cent. very little doubt attaches. The blood for analysis was obtained by venipuncture, great care being taken to render syringes, &c., calcium free and absolutely dry. All samples were withdrawn with the patient in the fasting state and at the same hour of the day (1 p.m. for skin cases, 8 a.m. for all others). All hospital cases received a diet containing an adequate calcium maintenance allowance.

Results and Discussions.

Group I.—Normals. Different observers give very varying figures for the calcium content of the serum, and while some, though differing from each other, find a fairly constant value, others show normal individuals differing from each other to such a degree that it is difficult to avoid the conclusion that faulty methods of analysis are in a large measure responsible for the variations. Thus Kramer and Tisdall (1) report ten normal cases with serum calcium from 9.5 to 10.5 mg. per 100 c.c. serum, six of them being between 9.5 and 10.0 mg.; and

¹ Received Oct. 21, 1925.

² Working under the tenure of a Beit Memorial Fellowship.

Kramer and Howland (2) give seven normals with the range 9.3 to 9.9 mg. calcium per 100 c.c. On the other hand, Watchorn (3) gives a distinctly higher range for the normal value (10.0 to 10.8 mg.), though here again the range is fairly small. Schamberg and Brown (4), in five normal cases, find values ranging from 9.7 to 11.3 mg. calcium per 100 c.c. serum. These variations, while they do not invalidate the conclusions drawn by each worker from his own results, render the comparison of tables by different authors a matter of some difficulty. Such comparison, however, may be facilitated—and, indeed, the justice of the author's deductions can only be appreciated—if each paper includes a series of analyses carried out on normal individuals by the method employed in abnormal cases.

For the present work, the normal value for the serum calcium was obtained by estimations on the sera of eight normal healthy men—laboratory workers and clinical assistants. The estimations were done in duplicate, excellent agreement being obtained, and gave results varying from 9.4 to 9.9 mg. calcium per 100 c.c. serum (Table I). This, for the purposes of the present paper, is taken as the normal range, values above 10.1 being considered as appreciably above normal, and values below 9.2 as subnormal.

TABLE I. *Normal Subjects.*

Case No.	Mg. Calcium per 100 c.c. Serum.
I	9.6
	9.7 (15 days later)
II	9.6
III	9.9
IV	9.5
V	9.6
VI	9.5
VII	9.5
VIII	9.7

Group II.—Skin diseases. Cases XXVIII to XXX show values for the serum calcium within the normal range, and agree with the observations of other workers (3, 4, 5). They are of interest from another point of view. Case XXVIII resembles Cases I–IV (Figs. 2 A and 2 B) in showing a very distinct rise of the serum calcium to well above normal values on administration of parathyroid, and a fall back to normal when the drug was withheld. Cases XXIX and XXX showed absolutely no variation of the serum calcium when calcium chloride or lactate was given by the mouth in doses of 4 gm. daily. This result, which is exhibited in other cases to be dealt with later, is in entire agreement with the findings of Denis and Minot (6), although Stewart and Haldane (7), amongst others, have shown that massive doses (30 gm.) of calcium chloride are capable of raising the serum calcium to a level 25 per cent. above normal. It has, of course, been found possible (6, &c.) to raise a low calcium content to normal by administration of calcium salts, and several of our cases confirm this. In Case XXXI, where a low calcium level had been maintained for twenty days, combined calcium chloride and parathyroid administration succeeded in raising the serum calcium to a level slightly above the normal (Fig. 1).

Case XXVIII. F., aged 25, suffering from erythema induratum scrofulosorum; her second attack. Received parathyroid sicc. 0.013 grm. daily per os.

Case XXIX. M., aged 58, suffering from extensive varicose ulceration of the leg, of one year's duration. Received calcium chloride 4.0 grm. daily per os.

Case XXX. M., aged 23, suffering from psoriasis, widespread. Received calcium lactate 4.0 grm. daily per os.

Case XXXI. F., aged 30, suffering from generalized lupus erythematosus, intermittent fever present. Received parathyroid sicc. 0.013 grm. and calcium chloride 4.0 grm. daily per os.

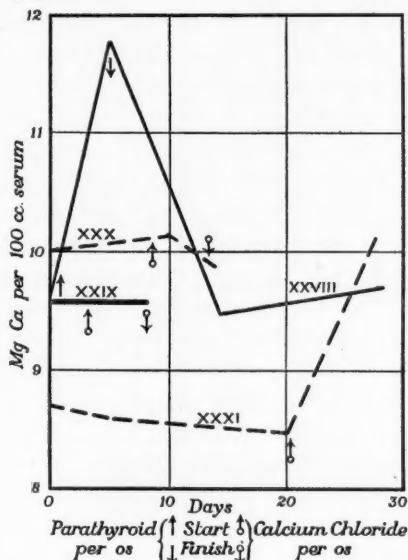


FIG. 1.

Group III.—Effect of parathyroid feeding. The results obtained in this group are shown graphically in Figs. 2 A, 2 B, and 2 C. Cases I, II, and IV (Fig. 2 A), after a period in which the serum calcium remained constant, were given a daily dose of parathyroid (0.013 grm. per os). The calcium immediately rose to a value far above normal, the maximum being reached in 2–9 days. In Cases I and IV this high level was maintained for 12–14 days, and, the parathyroid administration being then stopped, was followed by a gradual fall to a normal level. Case II left the hospital on the eleventh day, and was given calcium lactate (2.0 grm. daily) as well as parathyroid by her own physician. On this treatment her serum calcium remained high until the forty-sixth day, when all drugs were withdrawn. The calcium then fell to a value well below normal.

Case III (Fig. 2 B) is peculiar in that the calcium fell rapidly to a subnormal level while parathyroid was still being given. That this result is real is shown by the exactly similar finding in Cases V and VI. The further history of these cases is, unfortunately, somewhat obscure. Hypodermic injection of 0.013 grm. of parathyroid on each of two days was, in all three cases, followed by a return of

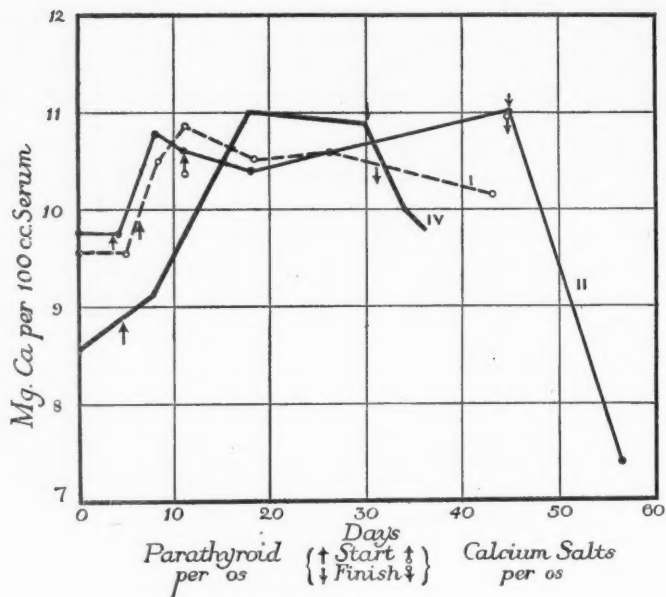


FIG. 2 A.

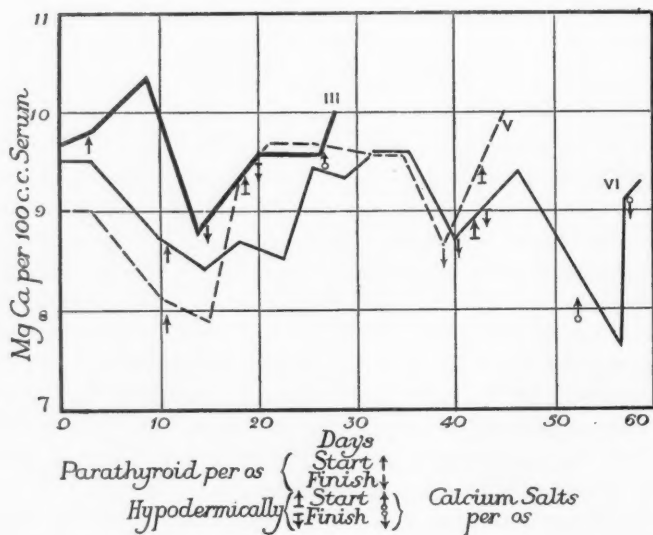


FIG. 2 B.

the calcium to a normal level, but the absence of an observation on the day immediately prior to the first injection renders it doubtful whether this rise is merely the normal rebound, or is directly due to the parathyroid. It will be noted, however, that in Case VI the rise after parathyroid injection is followed by a still more marked fall. Now, had the rise been due to normal physiological conditions, the calcium should have remained at the higher level, since the rise could only have been brought about by the tissues having made good their previous calcium depletion—the existence of which was evidenced by the low value before parathyroid injection. On the other hand, were the rise directly due to the parathyroid injection, one would expect that the tissues would be left still further depleted of calcium, so that cessation of the treatment would be followed by a drop in the serum calcium to a level as low as, if not lower than, the first. It may therefore be concluded that the second rise in Cases III, V, and VI was due to a mobilization of calcium brought about by the injected parathyroid. The hypothesis that the parathyroid influences the serum calcium by aiding the mobilization from the tissues is not, of course, essential to the argument. Whatever its action may be, and it is easy to suggest other possible mechanisms than the one postulated, it is evident that a temporary rise caused by parathyroid will, in all probability, be followed by a fall on removal of the stimulus, whereas an unaided rise will be permanent.

In Cases V and VI, the records start with a fall in the serum calcium extending over thirteen days, notwithstanding the fact that during part of this time the patients were receiving 0.013 gm. parathyroid daily by the mouth. It is significant that on the second day one patient (V) had received an intramuscular injection of 1,000,000,000 *B. coli*, whilst the other (VI) had $\frac{1}{2}$ c.c. of Armour No. 2 peptone intramuscularly; both, therefore, were presumably suffering from mild protein shock, although they showed no subjective or objective symptoms. The question again arises as to whether the subsequent rise is merely the normal physiological rebound or whether it is due to the parathyroid action. Probably both factors were responsible; as far as the parathyroid is concerned, it will be noted that the rise is followed by a second fall, so that the argument used in the preceding paragraph may again be used with a like conclusion.

Cases VII and VIII (Fig. 2 c) show no alteration whatever of the serum calcium over a period of sixteen and twelve days respectively in spite of a daily dose of 0.013 gm. of parathyroid by the mouth, and, moreover, they show no fall on cessation of the parathyroid administration. Furthermore, 2.0 gm. of calcium chloride t.i.d. for ten days produced no change in the serum calcium level of Case VIII. For this failure of the parathyroid to produce a rise in the serum calcium no explanation can be offered. The preparation used was the same as was given to Cases I–IV. In Case VII a contributory factor may have been the enormous amount of oedema, and the extreme cardiac and renal inefficiency.

Still more surprising, especially in view of Collip's recent work (8) on tetania parathyreopriva in dogs, is the remarkable consistency of the serum calcium

in Case XX (Fig. 2 c). The patient, a female aged 45, had thyroid and parathyroid glands removed on account of malignant disease. The B.M.R. was -11 per cent. prior to operation. Fifty-four hours after operation she developed tetany, lasting two hours, and received 5 c.c. of 10 per cent. solution of calcium chloride intravenously, along with parathyroid, 0.013 gm. per os. Sixty-four hours later tetany again developed, and lasted nine hours. Calcium chloride was given intravenously and parathyroid by the mouth. This treatment was continued for three days, when she had received parathyroid 0.085 gm. and calcium chloride 2.5 gm., and was then stopped. Between the attacks of tetany, and after treatment had been commenced, the serum calcium was 6.9 mg. per 100 c.c. During the succeeding fifty-two days the patient received parathyroid 0.013 gm. daily by the mouth, and for two periods of three days a preparation of parathyroid

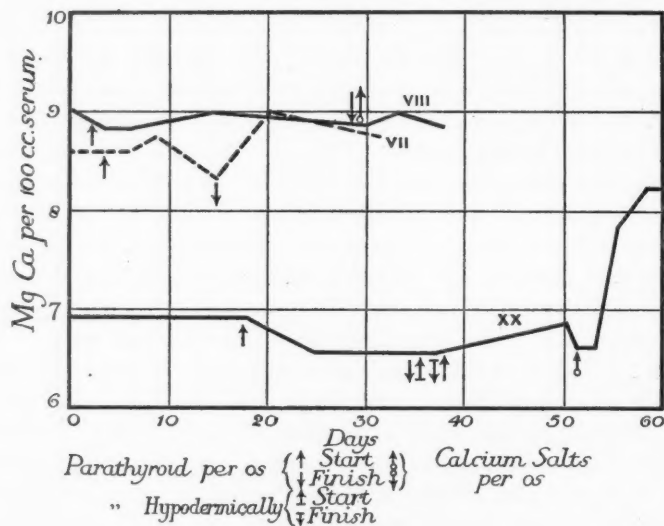


FIG. 2 c.

was given hypodermically. The serum calcium remained constant throughout, and, though there was no recurrence of tetany, Trousseau's and Chvostek's signs could always be elicited. On the fifty-third day, tetany developed spontaneously and lasted one hour. During this attack a sample of blood was taken for analysis, and, as is shown in Fig. 2 c, the serum calcium was found to be unaltered from the fifty-first day, when tetany was merely latent. Spontaneous tetany appeared again on the following day, but there was no further recurrence. Parathyroid was continued per os, and, following the tetany, 4.8 gm. calcium chloride were added daily. Trousseau's and Chvostek's tests remained positive. The B.M.R. soon after was -16 per cent.

Thus, while parathyroid is capable, in certain cases, of raising the serum calcium from a subnormal or normal level, and maintaining it at a level above the normal—an action which is augmented by the simultaneous administration of

calcium salts, and can occasionally only be elicited by the combined administration of the two factors—in other cases it appears to be without effect. In the absence of any knowledge of the mechanism involved in the raising of the serum calcium by parathyroid, it is impossible to offer any adequate explanation of these results. There are, however, indications that the action consists in the mobilization of readily available stores of calcium in the tissues, and that it can act, therefore, only when such stores are present.

Case I. F., aged 60, suffering from rheumatoid arthritis involving hands, wrists, shoulders, knees, and spine, of four years' duration. Joints became swollen periodically; movement limited and painful in affected joints; radiographs showed marked rheumatoid changes. Patient received parathyroid 0.013 grm. daily per os.

Case II. F., aged 21, suffering from rheumatoid arthritis affecting larger joints. Peri-auricular change marked, bony change slight. Condition commenced acutely five years ago, and there have been frequent recurrences of arthritic involvement. Patient had parathyroid 0.013 grm. daily and calcium lactate 2.0 grm. daily per os.

Case III. F., aged 35, suffering from neurasthenia. Complained of vague pains in scapular region and over abdomen; nothing objective, except that both kidneys were palpable. Reflexes exaggerated. Improved with rest. Patient had parathyroid 0.013 grm. daily per os, and, for three days, parathyroid 0.013 grm. daily hypodermically.

Case IV. F., aged 60, suffering from Raynaud's disease. No history of previous attacks. Fingers of one hand affected, preceded by period of under-nutrition. The process caused area of skin at tips of three fingers to slough. Patient received parathyroid 0.013 grm. daily per os, and, for three days, parathyroid 0.013 grm. hypodermically.

Case V. F., aged 40, suffering from rheumatoid arthritis of three years' duration. All large joints affected; X-ray shows peri-auricular and bony changes. Discharged markedly improved. Patient had injection of *B. coli* (1,000,000,000) during period of observation, parathyroid 0.013 grm. daily per os, and, for several days, hypodermic injections of parathyroid 0.013 grm.

Case VI. F., aged 49, suffering from rheumatoid arthritis affecting joints of hands and feet; both knee-joints swollen, painful, and stiff. X-ray shows bony and peri-auricular changes. Muscular atrophy present. Condition has advanced slowly during past six years. Swelling subsided considerably and pain disappeared during period of treatment. Had peptone injections (one during, and several subsequent to, period of observation), 0.013 grm. parathyroid daily per os, and, for several days, hypodermic injections of 0.013 grm. parathyroid daily.

Case VII. F., aged 54, suffering from bronchitis, chronic interstitial nephritis, and cardiac failure. Patient had marked oedema of the lower extremities, ascites, and oedema of the bases of the lungs. Death occurred two weeks after observations ceased. Patient had 0.013 grm. parathyroid daily per os.

Case VIII. F., aged 30, suffering from neurasthenia. Vague shooting pains in scapular and sacro-iliac regions; no cause discovered. Patient had 0.013 grm. parathyroid per os, and several hypodermic injections of 0.013 grm. parathyroid daily.

Group IV.—Nephritis. Marriott and Howland (9) have reported low values for the serum calcium in cases of nephritis accompanied by acidosis, while Denis

and Hobson (12) found a decreased serum calcium in only one-fifth of the cases examined. All cases of nephritis we have examined show a low serum calcium sufficiently long after admission to hospital for stabilization on the new diet to have taken place (Table II—Initial Values). We have, however, made no observations of the bicarbonate reserve or the CO_2 combining power. In three cases which have been followed up, there appears to be a rise in the serum calcium towards normal, coincident with a fall in the blood urea. This tendency may be accelerated by administration of calcium chloride, which may even produce a temporary rise of the serum calcium to slightly above the normal value (Fig. 3).

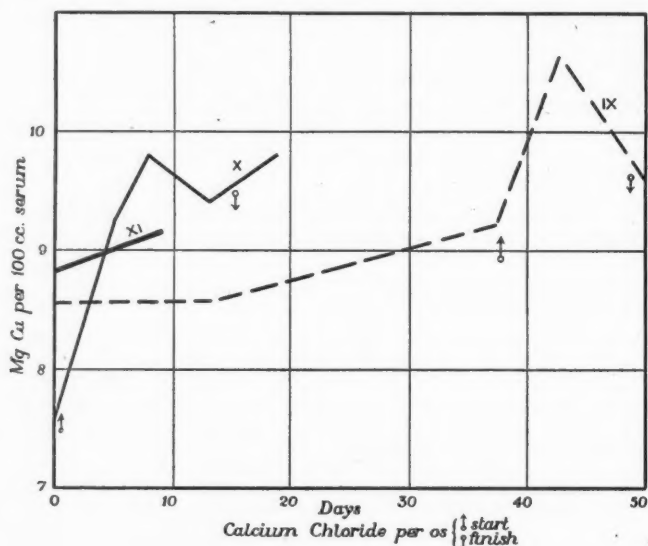


FIG. 3.

Case IX. M., aged 27, suffering from acute nephritis. Samples of blood taken throughout illness and convalescence. Patient had 1.5 gm. calcium chloride t.i.d.

Case X. F., aged 39, suffering from chronic nephritis, hydraemic type. Recurrent oedema of face and legs over a period of ten years; first attack was acute. Some facial oedema and albuminuria present. Condition cleared up under treatment. Calcium chloride given in doses of 4 gm. daily.

Case XI. M., aged 12, suffering from acute nephritis. Extensive subcutaneous oedema present. The first sample of blood was taken while symptoms were marked; the second when the oedema had disappeared, and blood and albumin were no longer present in the urine.

Group V.—Diabetes. In diabetes, with clinical ketosis and glycosuria, the serum calcium is low. Clinical improvement—absence of sugar and acetones from the urine, with lowering of the blood-sugar—is accompanied by increases in the serum calcium to normal values. Typical cases are shown in Fig. 4. These results are, of course, in agreement with those of Kahn and Kahn (10) and

of Loeper and Béchamp (11), who have found the serum calcium to be low in cases of diabetes accompanied by acidosis.

Case XV. M., aged 33, suffering from diabetes mellitus. Symptoms present for sixteen days, but had been getting thinner for some time. Ketonuria disappeared the day before the first calcium estimation; thereafter the urine remained free from acetone. Treatment consisted of dieting, with, in addition, 30 units of insulin *per diem*.

Case XVI. F., aged 60, suffering from diabetes mellitus of three years' duration. At the time of the first calcium estimation, ketonuria was present, but had completely disappeared before the second sample of blood was withdrawn. Treatment consisted of dieting, with, in addition, 20 units of insulin daily.

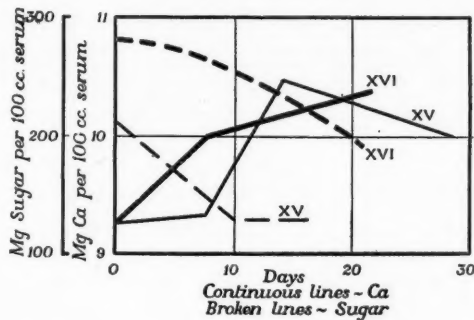


FIG. 4.

Group VI.—Endocrine cases. Case XXI was a cretin, aged 19 years, though his developmental condition was that of a child of 2 or 3 years of age. On admission, his serum calcium was 9.89 mg. per 100 c.c., an amount within the normal range. After three days, during which 0.6 gm. thyroid sicc. was administered, the calcium fell to 9.0 mg., while the B.M.R. rose from - 5 per cent. to + 37 per cent. A further twenty-four days of thyroid administration (5.5 gm. in all) resulted in a rise of the calcium serum to 13.2 mg. per 100 c.c., and of the B.M.R. to + 79 per cent. Unfortunately, in spite of the marked mental improvement accompanying these changes, it was found necessary to withhold thyroid for a period of fourteen days on account of emaciation, which was becoming severe. At the end of this period the serum calcium had fallen to 9.6 mg. per 100 c.c.—normal.

Cases XXII and XXIII were suffering from pituitary deficiency, resulting in the former case in infantilism, in the latter in obesity. Over a period of twenty-seven days, Case XXII showed no appreciable alterations in the serum calcium despite periods of pituitary and thyroid administration during which the B.M.R. remained constant. Case XXIII, starting with a somewhat low serum calcium and a B.M.R. of + 6 per cent., showed, after nine days, during the last four of which the patient had received 1.0 gm. of thyroid sicc. by the mouth, a serum calcium very slightly above the normal value, and a B.M.R. of + 14 per cent. During a further period of nine days the patient received 1.0 gm. of thyroid sicc.

per diem, and at the end of that time the serum calcium was practically unchanged. Two days later the B.M.R. was + 25 per cent. It would appear, therefore, that the thyroid exerts no direct action on the calcium content of the serum, but that it may, by its influence on the general metabolism, indirectly aid in raising it to a normal level (or above normal where, as in Case XXI, ossification is proceeding). Fig. 5 shows the results obtained in these cases.

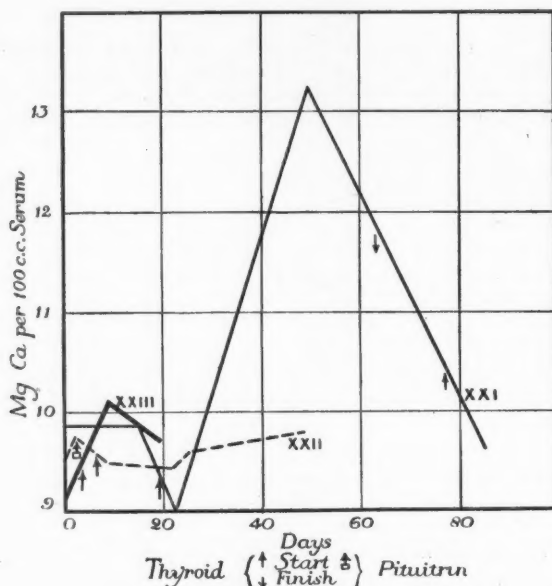


FIG. 5.

Case XXI. M., aged 19, typical cretin. Height, 3 ft. 4 in.; weight, 3 st. 9 lb.; several milk teeth not erupted; supraclavicular present; fontanelles patent; testicles lying in inguinal canals; B.M.R. - 6 per cent. (calculated on bases of actual age). X-rays show arrested development of epiphyses and vertebrae, and non-appearance of secondary centres of ossification. Ext. thyroid. sicc. given by the mouth in increasing doses. Marked clinical improvement, loss of myxoedematous tissue, testicles descended, two teeth erupted, brighter.

Case XXII. M., aged 18. Development arrested after 14 years of age; Clinical condition, one of infantilism, due to pituitary deficiency. Height, 4 ft. 6 in.; weight, 4 st. 12.5 lb. Treatment: liq. pituitrin given by means of nasal plugs for a few days, then the dry extract of the anterior lobe given by the mouth along with ext. thyroid. sicc. No improvement.

Case XXIII. F., aged 32, complained of increasing obesity for past ten years. Present condition: obesity of hypopituitary type; patient had not menstruated for fourteen months. Treatment: low caloric diet (795 cal. *per diem*), increasing doses of ext. thyroid. sicc. (up to 0.6 gm. *per diem*), and ext. pituitary, anterior lobe. Result: slight loss in weight, return of menstruation.

Group VII.—Epilepsy. The cases used in this group were being employed in an investigation into the effect of a ketosis-producing diet on the incidence of fits. From our point of view, two points of interest seemed likely to emerge;

first, the relation between the incidence of fits and the serum calcium; and second, the effect of a ketosis on the calcium content of the serum.

Although, with one exception, only out-patients were available, it was found possible on three occasions to obtain blood samples within two hours of seizure, and in two further cases within fifteen hours. The results from these samples fail to show any constant variation from the normal.

The fact that subnormal values for the serum calcium have been reported in both nephritis (9) and diabetes (10, 11) when acidosis is present, suggests that it is the acidosis which is responsible for the lowered calcium, and, indeed, Vines (13) states that calcium loss always seems to accompany acidosis. On the other hand, Stewart and Haldane (7) found that in an acidosis produced by ammonium chloride ingestion, or by carbon dioxide breathing, the serum calcium was raised. Their experiments, however, were of short duration, and it may therefore be suggested that there is actually a preliminary rise with increased excretion (14), followed, as the immediately available stores of calcium become depleted, by a slow fall to subnormal values.

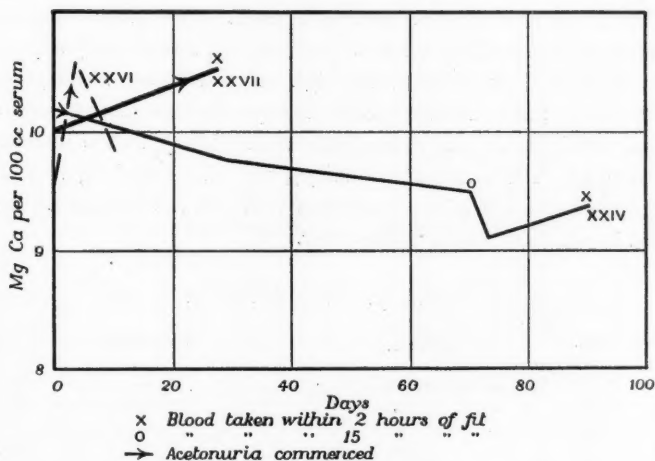


FIG. 6.

In Case XXIV, as is shown in Fig. 6, a high initial calcium was gradually lowered over a period of ninety days by a diet containing a fat-carbohydrate ratio sufficiently high to produce acetonuria. Unfortunately, it was not possible to obtain a blood sample until the patient had been receiving this diet for twelve days, by which time the preliminary rise, if such exists, was over. An observation during the early stages of acetonuria was, however, obtained in Case XXVI. The initial value of the serum calcium was perfectly normal—9.45 mg. per 100 c.c.—and this, after three days of acetonuria, rose to 10.6 mg. per 100 c.c. with a subsequent fall to normal, when observations were, perforce, discontinued. The evidence is thus admittedly slight, and requires much amplification before it is capable of yielding definite conclusions. It does, however, lend some support

to the suggestion outlined above as to the variations of the serum calcium during acidosis.

Case XXIV. F., aged 24. Epileptic seizures commenced when 14 years of age, occurring about once a week. During past few months fits have become more frequent, sometimes two or three on the same day. Consciousness is lost, and frequently injuries have been sustained during the fits. Treatment by acetonuria-producing diet; acetonuria kept constant on a carbohydrate-fatty acid ratio of 1:1.7. No improvement in condition.

Case XXV. F., aged 15. Major epileptic seizures at short intervals for past seven years, increasing in frequency recently. Put on diet having G.:F.A. ratio of 1:1.7, traces of acetone in urine daily. Fits not influenced.

Case XXVI. M., aged 19. Major epileptic fits once weekly for past year. Distinct relationship between fits and ingestion of large amounts of carbohydrate. Put on diet containing G.:F.A. ratio of 1:1.7. Acetone in urine after first day.

Case XXVII. F., aged 19. Major epileptic seizures monthly, related to periods, for six years. Patient was observed for twenty-seven days, no special diet or drugs being given.

Group VIII.—Initial values. Table II gives the values obtained for the serum calcium in a number of miscellaneous cases. Since the normal value, from our observations, ranges from 9.4 to 9.9 mg. per 100 c.c., the majority of the skin cases investigated show a somewhat high serum calcium, although some are within the normal range, and three cases of lupus erythematosus gave distinctly low values. This result is in some degree contradictory to the observations of Watchorn (3), of Urbach and Simhandl (5), and of Schamberg and Brown (4). Taking the results on the whole, it appears that variations from the normal are as frequent in one direction as in the other.

TABLE II. *Initial Values.*

Case No.	Sex.	Disease.	Comments.	Mg. Ca. per 100 cc. Serum.
I	F	Rheumatoid arthritis	—	9.3
II	F	" "	—	9.7
V	F	" "	—	9.0
VI	F	" "	—	9.5
XV	M	Diabetes mellitus	Ketonuria present	9.2
XVI	F	" "	" "	9.3
XVII	F	" "	" "	9.3
XVIII	F	" "	" "	9.16
VII	F	Chronic interstitial nephritis	Heart failure present	8.6
XII	M	" " "	—	8.7
XIII	F	" " "	—	8.2
XIV	F	" " "	Uraemic	8.0
IX	M	Acute nephritis	—	8.6
XI	M	" "	Marked oedema	8.9
X	F	Chronic "parenchymatous nephritis	—	7.5
XXII	M	Pituitary deficiency	Infantilism	9.5
XXIII	F	" "	Obesity	9.2
LV	M	Addison's disease	Symptoms of 3 months' dura- tion	11.0
XXI	M	Cretinism	—	9.9
XX	F	Tetania parathyreopriva	—	6.9

TABLE II (continued).

Case No.	Sex.	Disease.	Comments.	Mg. Ca. per 100 c.c. Serum.
XXIV	F	Idiopathic epilepsy	—	10.2
XXV	F	" "	—	10.0
XXVI	M	" "	—	9.45
XXVII	F	" "	—	10.0
XXIX	M	Psoriasis	—	10.0
XXXI	M	"	Receiving artificial helio- therapy	10.0
XXXII	F	"	Spreading	10.4
XXXIII	F	"	"	11.2
XXXIV	M	Pityriasis rubra	—	12.0
XXXV	M	" "	—	11.2
XXXVI	M	" "	—	9.8
XXXVII	M	Varicose dermatitis	—	13.0
XXXVIII	M	" "	—	12.7
XXXIX	M	Chronic leg ulcer	Duration: 1 year. Wasser- mann + + +	12.0
XL	M	" " "	Recently healed	11.5
XLI	M	" " "	Wassermann negative	10.2
XLII	F	" " "	" "	9.6
XXVIII	F	Erythema induratum scrofu- losorum	—	9.5
XLIII	F	Papulonecrotic tuberculide	—	8.5
XXX	F	Lupus erythematosus	Generalized. Died 6 weeks later	8.0
XLIV	F	" "	Face affected	8.6
XLV	M	" "	Long standing. Large area of face affected	9.0
XLVI	F	Erythema pernio	—	9.4
XLVII	F	Erythema multiforme	Due to cod-liver ingestion	10.4
IV	F	Raynaud's disease	—	8.5
XLVIII	F	Syphilis	Gumma. Wassermann + + +	10.9
XLIX	M	"	After 13 injections N. A. B.	10.0
L	M	"	Wassermann + + +	11.0
LI	F	Purpura	—	6.9
LII	M	Epistaxis	Recurrent, severe	10.2
III	F	Neurasthenia	—	9.7
VIII	F	"	—	9.0
LIII	M	Severe dyspepsia	Achlorhydric type. Neuras- themic	9.1
XIX	M	T. B. meningitis	Extensive tuberculous in- volvement of meninges found <i>post mortem</i>	7.15
LIV	M	Sciatica	Very intractable. No arthritic changes	9.2

Summary.

Using the method of Kramer and Tisdall (1) for the estimation of calcium in the blood-serum, the normal range was found to be 9.4 to 9.9 mg. calcium per 100 c.c. serum. In four cases, parathyroid administration raised the serum calcium to a level above the normal, and maintained it until the drug was

withheld. In three further cases the serum calcium was raised by parathyroid administration, but fell to subnormal values while the drug was still being given. In two cases parathyroid administration was without effect. In certain cases the effect of the parathyroid was augmented by giving calcium salts; in one case, however, even combined parathyroid and calcium administration was without effect.

In a case of tetania parathyreopriva (Case XX) parathyroid given over a prolonged period failed to influence the very low serum calcium value. When, however, calcium chloride was given in addition to parathyroid the serum calcium, while not reaching the normal level, rose considerably.

The administration of calcium salts alone by the mouth failed to produce any increase in the serum calcium in two cases in which the initial value was normal. In two other cases in which a rise was obtained, the initial value was low.

In three different types of endocrine deficiency no effect on the serum calcium which could be directly attributed to the administration of the deficient hormone was noted.

The effect of ketosis on the serum calcium was followed in cases of diabetes mellitus, and in cases of epilepsy in which the condition was induced by dietary measures. In the presence of ketosis the serum calcium was found to be subnormal except during the first days of the condition, when a high calcium was found. No constant relationship between the amount of serum calcium and the occurrence of fits was observed in the case of epileptics.

A table of serum calcium values in various disorders is given. Normal values have been found in chronic ulcerative conditions, while in three cases of lupus erythematosus the value is distinctly subnormal.

The authors wish to thank Prof. D. Murray Lyon for the interest he has taken in this work, and for his kindness in placing the necessary cases at their disposal. Certain of the expenses incurred during the investigation were defrayed by a grant from the Moray Fund of this University, hereby gratefully acknowledged.

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THE PURGATIVE ACTION OF MAGNESIUM SALTS¹

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DURING the last seventy years, many papers have appeared dealing with the mode of action of the saline purgatives. The experimental evidence advanced in support of the various theories put forward has been almost entirely indirect and, in many cases, conflicting.

The investigations recorded in this paper offer direct evidence (1) that the oral administration of purgative doses of magnesium sulphate is unaccompanied by any rise in the magnesium content of the blood-serum; (2) that a considerable increase (50–100 per cent.) in the magnesium content of the blood-serum produced by intramuscular injection of magnesium sulphate is unaccompanied by the characteristic purgative effect which follows the oral administration of this salt.

Brief Historical Sketch.

In the literature, two main theories concerning the mode of action of the saline purgatives are to be found.

The first (Buchheim (1, 2)) suggests that the action is entirely *local*, i.e. is exerted solely from the lumen of the intestine. It states that the ions known to produce catharsis, e.g. magnesium sulphate, phosphate, citrate, lactate, tartrate, &c., are not readily absorbed from the alimentary canal. When they are administered by mouth, sufficient liquid is retained in the intestine to maintain the contents isotonic with the blood (Wallace and Cushny (3)). This liquid is derived (1) from the liquid ingested; (2) from the intestinal secretions; and, (3) if the salts are given in concentrated solutions, by osmotic transference of liquid from the tissues and blood. The greater fluidity and bulk of the faeces results in acceleration of their passage through the intestine, thus catharsis is produced.

The second theory, first presented by Aubert (4), suggests that, on the

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contrary, the saline purgatives act, not from the lumen of the gut, but only after absorption of the cathartic ions.

Comparatively early in the history of the various theories, an attempt was made to determine the action of the saline purgatives when administered parenterally. Catharsis was reported to occur after intravenous, intramuscular, and hypodermic administration by some observers (Aubert (4), MacCallum (5), Bancroft (6), &c.); most observers, however, taking proper precautions to exclude the effect produced by exposure of the intestine, failed to observe any cathartic effect (Buchheim (1, 2), Auer (7, 8), Meltzer and Auer (9), Frankl (10), Mendel and Benedict (11)). In the case of magnesium, Joseph and Meltzer (12) found that peristalsis was inhibited by the intravenous or intramuscular injection of its salts. These negative results from parenteral administration are regarded by advocates of the second theory as 'not without fallacies, because it was a most abnormal condition to get the body fluids suddenly overwhelmed with excess of salts' (Hertz (13)).

Loeb's discovery that those salts which increase the $\frac{\text{Na}}{\text{Ca}}$ ionic ratio of the nutrient medium, especially those which precipitate calcium, increase the irritability of muscular tissue, added fresh interest to the second theory, inasmuch as many of the saline cathartics, e.g. sulphates, carbonates, citrates, tartrates, phosphates, &c., form compounds with calcium of only slight solubility or of feeble ionic dissociation. At the instigation of Loeb, MacCallum (5) reinvestigated the problem and concluded, from his experiments on rabbits, that the saline purgatives acted 'not only when introduced into the intestine, but also when injected subcutaneously or intravenously. *The presence of the salt in the lumen of the intestine is not necessary for its cathartic action . . . the salt must be absorbed into the blood before it can act on the intestine.*' Auer (7, 8), in a similar series of experiments, was unable to confirm either the original experiments of MacCallum or those subsequently carried out by Bancroft (6), and offered strong testimony that 'Moderate doses of the saline cathartics exert no purgative action when injected subcutaneously or intravenously', a statement confirmed by the experimental work of Frankl (10) in an almost contemporary paper.

In 1909 Hertz, Cook, and Schlesinger (13) approached the problem from a different standpoint. They showed first, by observation on a patient with a fistula of the ileum, that an insoluble bismuth salt travelled along the intestine quite as rapidly as the purgative salt. A Seidlitz powder was administered together with bismuth oxychloride to each of three individuals and the rate of passage along the alimentary tract was observed (1) by X-rays, and (2) by the time of appearance of the caecal sounds. Analyses of faeces and urine after the administration of magnesium sulphate were also made. Their results indicated that the rate of passage of the bismuth salt along the alimentary tract to the caecum (normally reached in about four hours after a meal) was only slightly, if at all, accelerated by the administration of a saline purge, although a fluid motion occurred in each case $1\frac{1}{2}$ to $1\frac{3}{4}$ hours after taking the salt. Moreover, they found

that the abundant watery stool, passed as a result of the saline purge, contained less sulphate than a normal solid stool passed the next day.

Padtberg (14), working on cats and employing the X-ray method, disputed the above results. He found that the administration of magnesium sulphate definitely increased the rate of passage of the bismuth meal through the intestine. Ury (15), in his experiments, found 50-70 per cent. of the magnesium sulphate administered in the first diarrhoeic stool; and carmine, given at the same time as the purgative, was present in the first motion.

It will be seen from the above historical sketch that the evidence is too conflicting, and that the methods employed to solve the problem are too indirect to justify definite conclusions.

The introduction of an accurate method for the estimation of magnesium in small quantities of serum (Cohen (16)) has made it possible to approach the problem along other lines, i.e. by direct determinations of the magnesium content of the serum after magnesium sulphate has been administered (1) by the mouth, and (2) by intramuscular injection.

Experimental Results.

(a) *The effect of the oral administration of magnesium sulphate in purgative doses (20-30 grm.) on the magnesium content of the blood-serum.*

Case I. T. S., 19 years. Male. Cerebellar tumour.

Dose: 20 grm. of crystalline MgSO_4 in 100 c.c. water.

Effect on serum:

		Magnesium Content of Serum (in mg. per 100 c.c.).
Before MgSO_4		2.66
1 hr. 0 min. after MgSO_4 (oral)		2.57
2 " 25 " " " "		2.63
3 " 20 " " " "		2.64
4 " 15 " " " "		2.58
5 " 20 " " " "		2.57

Purgation: Typical diarrhoeic stools occurred 2 hr. 35 min. and 4 hr. 35 min. after MgSO_4 .

Case II. M. H., 21 years. Female. Post-encephalitic Parkinsonism.

Dose: 20 grm. of crystalline MgSO_4 in 100 c.c. water.

Effect on serum:

		Magnesium Content of Serum (in mg. per 100 c.c.).
Before MgSO_4		2.78
0 hr. 45 min. after MgSO_4 (oral)		2.78
1 " 30 " " " "		2.71
2 " 25 " " " "		2.66
3 " 35 " " " "		2.66
4 " 25 " " " "		2.73

Purgation: Watery stool at 3 hr. after MgSO_4 .

Case III. W. G., 42 years. Male. Tabes optica.

Dose: 30 grm. of crystalline MgSO_4 in 100 c.c. water.

Effect on serum:

						Magnesium Content of Serum (in mg. per 100 c.c.).
Before MgSO_4						2.47
0 hr. 15 min. after MgSO_4 (oral)						2.46
0 " 30 "	"	"	"	"	"	2.48
1 " 5 "	"	"	"	"	"	2.52
1 " 35 "	"	"	"	"	"	2.49
2 " 5 "	"	"	"	"	"	2.58
3 " 0 "	"	"	"	"	"	2.58
4 " 0 "	"	"	"	"	"	2.54

Purgation: Typical diarrhoeic stools occurred 50 min., 2 hr., 2 hr. 35 min., and 3 hr. 35 min. after MgSO_4 .

It will be seen from the above cases (Fig. 1) that the oral administration of magnesium sulphate in purgative doses is, within the limits of experimental error, unaccompanied by any alteration in the magnesium content of the blood-serum.

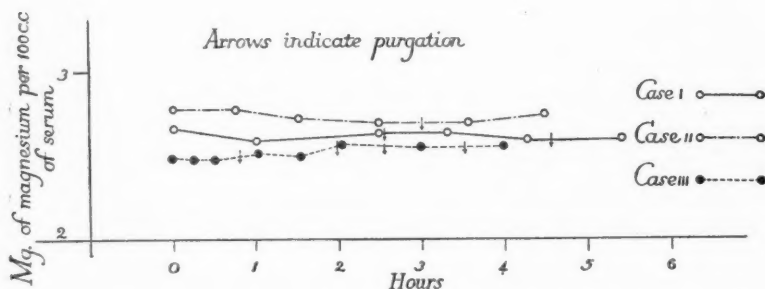


FIG. 1 Effect of the oral administration of MgSO_4 on the magnesium content of the serum.

(b) The effect of intramuscular injection of magnesium sulphate on the magnesium content of the blood-serum, and on the action of the bowels.

Case I. Male, 43 years. Post-encephalitic myoclonus.

Dose: 18 c.c. of a 10 per cent. solution of MgSO_4 intragluteally.

Effect on serum:

						Magnesium Content of Serum (in mg. per 100 c.c.).
Before MgSO_4						2.41
1 hr. 30 min. after MgSO_4 (intramuscular)						3.28
2 " 15 "	"	"	"	"	"	4.94
3 " 45 "	"	"	"	"	"	2.86
5 " 15 "	"	"	"	"	"	2.71
6 " 0 "	"	"	"	"	"	2.54
27 " 0 "	"	"	"	"	"	2.37

Effect on bowels: This patient had six injections of 10 per cent. MgSO_4 , starting with 10 c.c. and increasing by 2 c.c. daily. During the course he had no diarrhoea and no watery stools; he stated he was 'rather costive' during this time.

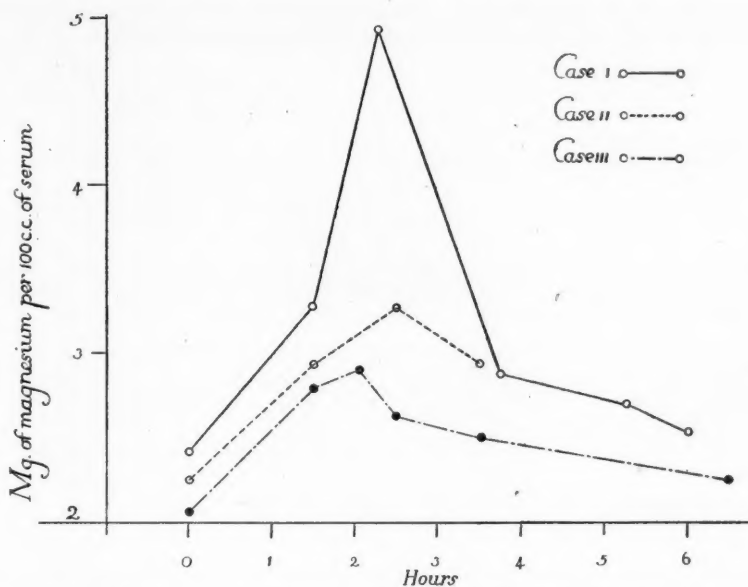


FIG. 2. Effect of intramuscular injection of MgSO_4 on the magnesium content of serum.

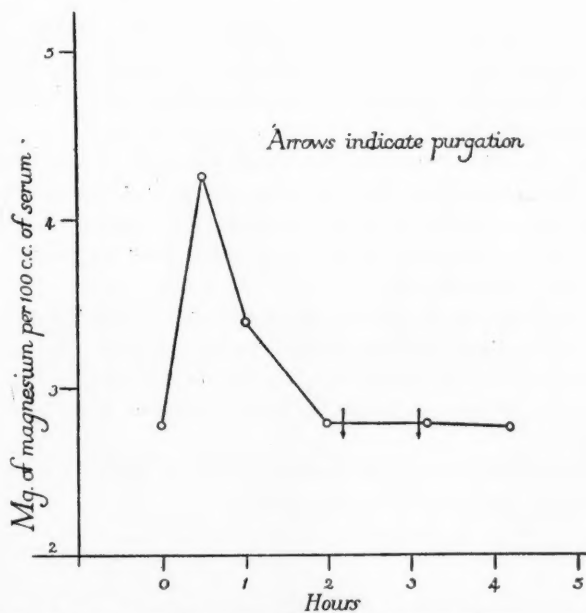


FIG. 3. Effect of the oral administration of MgCl_2 on the magnesium content of the serum.

Case II. F. H., male, 19 years. Post-encephalitic Parkinsonism with tremor.
Dose: 20 c.c. of a 10 per cent. solution of MgSO_4 intragluteally.

Effect on serum:

					Magnesium Content of Serum (in mg. per 100 c.c.).
Before MgSO_4					2.25
1 hr. 30 min. after MgSO_4 (intramuscular)	2.94
2 " 20 " " " "	3.29
3 " 30 " " " "	2.94
6 " 0 " " " "	2.54

Effect on bowels: No motion occurred on day of injection. This patient had a course of injections similar to those detailed in Case I. No increased looseness of the bowels ensued.

Case III. B. B., female, 41 years. Neurosis.

Dose: 20 c.c. of a 10 per cent. solution of MgSO_4 intragluteally.

Effect on serum:

					Magnesium Content of Serum (in mg. per 100 c.c.).
Before MgSO_4					2.07
1 hr. 35 min. after MgSO_4 (intramuscular)	2.80
2 " 5 " " " " "	2.90
2 " 30 " " " " "	2.63
3 " 30 " " " " "	2.49
6 " 30 " " " " "	2.25

Effect on bowels: Patient had a daily motion of the bowels before the day of injection; no motion on the day of injection; normal motion on the next day.

The above three cases (Fig. 2) are typical examples selected from a series of twelve submitted to intramuscular injections of magnesium sulphate. They illustrate the higher and lower limits of the magnesium values in the blood-serum following such injection.

The experimental observations detailed above show that a considerable increase (50-100 per cent.) in the magnesium content of the blood-serum may be produced by intramuscular injection of magnesium sulphate; this rise was, however, in no case accompanied by the characteristic purgative effect of the salt when given by mouth.

Since the sulphate anion in magnesium sulphate is itself purgative, it might be held that in purgation the magnesium ion plays no part. That this objection does not hold good is, however, shown by the cathartic action of such salts of magnesium as the chloride, in which, so far as purgation is concerned, the anion is indifferent.

When a purgative dose of magnesium chloride is given by the mouth, a rise in the magnesium content of the serum ensues.

Case I. Male, 25 years. Normal.

Dose: 20 grm. of MgCl_2 in 100 c.c. water.

Effect on serum:

						Magnesium Content of Serum (in mg. per 100 c.c.).
Before MgCl_2						2.77
0 hr. 30 min. after MgCl_2 (oral)	4.25
1 " 2 " " " "	3.87
1 " 58 " " " "	2.79
3 " 10 " " " "	2.77
4 " 10 " " " "	2.75

Effect on bowels: Copious, watery motions occurred at 2 hr. 10 min. and 3 hr. 5 min. after the salt was taken.

It will be observed that the rise in the magnesium content of serum following a purgative dose of MgCl_2 is no higher and no less rapid than that following intramuscular injection of MgSO_4 . Since the latter does not cause purgation it is improbable that the purgative effect of MgCl_2 could be due to the absorption of the magnesium ion.

That some salts of magnesium must be absorbed into the blood is evident, for magnesium is an element essential to the growing organism (e. g. in ossification). In connexion with the non-absorption of magnesium from the alimentary tract when MgSO_4 is administered orally, it is of interest to recall Hamburger's observation (17) that contact of the intestinal epithelium with magnesium sulphate hindered the subsequent absorption even of common salt.

A further point of interest in connexion with the absorption of MgSO_4 from the alimentary canal is the series of cases on record in which the administration of Epsom salts has been followed by symptoms of poisoning or death. Fraser (18) has collected six cases from the literature and has added one of his own. A careful study of these seven cases, however, reveals no evidence suggesting symptoms known to be due to magnesium intoxication. Rather do they suggest marked local gastric or intestinal irritation with resulting shock and syncope.

Summary and Conclusion.

The observations recorded above afford direct evidence that the purgative action of magnesium salts is exerted independently of the absorption of magnesium into the blood.

I wish to express my thanks to Dr. W. J. Dilling for many important references.

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ON THE HYDROGEN-ION CONCENTRATION AND SOME OTHER PROPERTIES OF THE BLOOD FROM TWO CASES OF AUTOTOXIC ENTEROGENOUS CYANOSIS¹

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Autotoxic Enterogenous Cyanosis.

THE publication of a posthumous article by Stokvis (1902) first drew attention to a condition of cyanosis which he called 'Autotoxic Enterogenous Cyanosis'. Since then there have been a number of similar cases recorded. The investigations of these cases have been chiefly confined to the detection of abnormal forms of haemoglobin such as methaemoglobin and sulph-haemoglobin, and to the bacteriological examination of the blood. The oxygen capacity and content of the arterial blood and the physico-chemical behaviour of oxyhaemoglobin in such cases have not as yet been reported. During the past two years such an opportunity has been offered and is here briefly recorded.

Case I. Mrs. A. B., aged 31. This patient was admitted to the Royal Infirmary, Edinburgh, in the service of Professor Lovell Gulland, on June 4, 1920. She complained of vomiting, abdominal pain, breathlessness, and palpitation. The patient for many years had suffered from attacks of 'biliousness', which, however, left no ill effects. In 1917 she began to have pain across the abdomen, with vomiting, immediately after meals. This was followed by the development of cyanosis. The vomiting relieved the pain, and the attacks, after lasting for a few days, were followed by a period of comparative good health. The attacks became more frequent but less severe, while the cyanosis became more or less constant. The pain and vomiting were not conspicuous, provided her meals consisted of semi-fluid food in small amounts. There was no constipation or diarrhoea. The examination of heart and lungs showed nothing abnormal; the liver was found to be slightly enlarged, the edge being palpable $1\frac{1}{2}$ cm. below the costal margin. The spleen was found not to be enlarged. The cyanosis was particularly pronounced in the skin of the face and hands and to a lesser extent over the body generally. There was very pronounced cyanosis of the mucous membrane of the lips and buccal cavity. The urine and faeces were microscopically normal. An exhaustive inquiry into the intestinal flora was not undertaken. A blood-culture gave a negative result.

¹ Received July 11, 1925.

X-ray examination of the gastro-intestinal tract gave the following results:

1st meal. Trace in caecum and low coils of ileum.

2nd meal. Good J-stomach with slight alteration of cap because of close proximity to liver—possibly adhesions. Stomach was highly tonic.

2nd day. Colon filled to mid descendens. Note high tenacity and well-marked canalized appendix.

3rd day. Whole colon traced—appendix still well canalized. Both flexures apparently on same level.

Case II. F. R., female, aged 43. Occupation, dressmaker. This patient was admitted to the Royal Infirmary on October 14, 1922. As a child she had apparently suffered from some 'bowel trouble' which gave little or no disability. Although she had never been robust she had at no time had a serious illness up to the age of 33, when she suffered from peptic ulcer. She was treated for this and made pronounced improvement, although she repeatedly had haematemesis of small amount. In the spring of 1921 she developed obstinate constipation. Following this she became very anaemic and in a few months' time developed diarrhoea. Up to the time of admission she constantly suffered from complaints referable to the gastro-intestinal tract. There was intermittent constipation and diarrhoea, thirst, epigastric discomfort after eating, which in an hour or so developed into pain, most pronounced in the left hypochondrium. Associated with this there was breathlessness, palpitation, heartburn, nausea, and flatulence. This was not relieved until the bowels moved. Vomiting was frequent within half an hour of taking food and was more pronounced when patient was going about than when at rest.

On physical examination the most striking feature was the conspicuous cyanosis of the cheeks, lips, and hands, with a general cyanosis of the limbs and trunk. The extremities were apt to be cold and the circulation was apparently poor. Examination of heart and lungs revealed no abnormality. The arteries were soft, pulse-rate 78; blood-pressure: systolic 123 mm. Hg, diastolic 82 mm. Hg. Abdomen was scaphoid and flaccid, no visible peristalsis, no resistance, but some tenderness in left hypochondrium. Liver and spleen were normal in size. A barium meal showed the greater and lesser curvature of the stomach to be at the average level and the duodenal cap was normally visible. At the end of six hours there were still traces of barium in the pyloric portion of the stomach and in the duodenum, the caecum not having been reached. 'A good example of small intestine stasis is visualized as if some reflex cause were at work.' At the end of twenty-four hours the small intestine was empty while the caecum and colon were still filled. Blood-culture on two occasions gave no growth. The urine and faeces were normal to the usual tests. In the faeces the food-particles were well digested, there was no excess of fat, and occult blood was not found.

Both of these cases appeared to be typical of the condition first named by Stokvis as autotoxic enterogenous cyanosis. It was thought advisable, therefore, to make an extensive examination of the blood, particularly in regard to the oxygen saturation of the arterial blood, the oxyhaemoglobin curve, the carbon dioxide combining power, and the hydrogen-ion concentration.

Examination of the Blood.

As will be seen in Table I, the red cell count in both cases closely approximated to the normal. In both cases the oxyhaemoglobin estimations were determined with difficulty. The laked blood converted into CO-haemo-

globin assumed a pink colour with yellowish-green tint, so that it was impossible to make an accurate comparison with the standard solution. This difficulty of colorimetric estimation of the haemoglobin was considered to be due to the presence of sulph-haemoglobin as determined by spectroscopic examination. This pigment was apparently present in very small concentrations in comparison to the oxyhaemoglobin, as it was only when very strong solutions were examined that the bands of sulph-haemoglobin were identified.²

TABLE I. *Tabulation of the Results obtained in the Two Cases reported.*

Observations.	Case I.	Case II.
Red blood count	5,960,000	4,450,000
Oxyhaemoglobin	80 % *	72 % *
Colour index	0.73	0.81
White blood count	3,430	4,500
Methaemoglobin	Not found	Not found
Sulph-haemoglobin	Present	Present
Oxygen saturation of arterial blood	91 %	88 %
CO ₂ content of arterial blood	40 c.c. vol. %	37 c.c. vol. %
Oxygen capacity of arterial blood	14.9 c.c. vol. %	15.2 c.c. vol. %
Oxygen saturation of venous blood, arm at 15° C. without artificial stasis	47 %	24 %
Oxygen saturation of venous blood, arm in hot water at 46° C. for 30 minutes	—	82.6 %
CO ₂ content of venous blood, arm in hot water at 46° C. for 30 minutes	—	48.4 c.c. vol. %
Alveolar air CO ₂ pressure	39 mm.	33 mm.
Alveolar air O ₂ pressure	107 mm.	110 mm.

* On account of the yellowish appearance of the laked blood when converted into CO-haemoglobin, an accurate haemoglobin determination by the Haldane method was impossible, and these figures represent a doubtful but average estimation.

The presence of abnormal combinations of haemoglobin did not seem to be sufficient to account for the degree of cyanosis which was present in either case. It therefore seemed important to determine the oxygen saturation of the arterial blood. This was found to be distinctly below the normal saturation. In Case I it was 91 per cent. and in Case II it was 88 per cent. The carbon dioxide content of the arterial blood in these cases was found to be 53 and 47.3 volumes per cent. respectively. The relation of this finding in Case I to the alveolar air and carbon dioxide dissociation curve will be discussed later.

The total oxygen capacity of the arterial blood was determined in order that it might be compared with the oxygen capacity as theoretically estimated by the oxyhaemoglobin percentage. In Case I the oxygen capacity by the ferricyanide method was found to be 14.9 c.c. volumes per cent. This would correspond to an oxyhaemoglobin content of 80.5 per cent., which very closely agrees with the actual finding of 80 per cent. In Case II, however, the oxygen capacity was 15.2 c.c. volumes per cent., representing an oxyhaemoglobin content of 82 per cent. The oxyhaemoglobin estimation by the Haldane method, however, was

¹ Nitrites have been found in the blood of such cases by van den Bergh and Grutterink (1906), which was confirmed by Gibson and Douglas (1906). Mr. Robson made a careful study of this point in Case II, but was unable to demonstrate any increased nitrite reaction as compared with the normal controls.

only 72 per cent. In both cases the haemoglobinometer readings were indefinite on account of the difficulty of comparison with the normal as already referred to.

The diminished oxygen saturation of the arterial blood could not be explained by an obvious lesion of the lungs which might interfere with the complete aeration of the blood as it passed through the pulmonary capillaries. It seemed necessary, therefore, to determine if the haemoglobin possessed any characteristics which interfered with the normal dissociation of oxyhaemoglobin. This was accomplished by determining the oxyhaemoglobin dissociation curves of the two cases, and in addition, in Case I, a very complete investigation was made into such properties of the blood as hinge about the hydrogen-ion concentration.

The blood was drawn from the median basilic vein without stasis (at 6.30 p.m.) into a beaker, defibrinated, and transferred to a glass-stoppered bottle, all under strictly aseptic precautions. The bottle was then immersed in a metal receptacle containing crushed ice, and was so supported by metal ridges as to prevent any movement through partial melting of the ice. The tin container was surrounded by non-conducting material and the whole placed in a wooden box. It was dispatched from Edinburgh to London by the night train, being met at London and immediately taken to Cambridge, where it arrived shortly after 11 a.m. Here it was found that the ice had not completely melted. The observations were then immediately started.

The question arises, To what extent does the blood alter during its journey whilst in ice storage? The answer is to be found in Figs. 6 and 7. Fig. 7 shows the dissociation curve at 40 mm. CO_2 pressure drawn from the value of K given for that CO_2 pressure in Fig. 6 ($I/K = 2,900$; $K = 0.000345$). The data from which Fig. 6 was obtained were compiled from investigations made in Cambridge from blood collected in May 1923, the blood in each case being withdrawn the night before. The points on the figure were obtained from A. B.'s blood in Edinburgh, the analysis commencing immediately after the blood was defibrinated: that is, some ten minutes after it was withdrawn. These determinations were made on July 23, 1920. The two sets of determinations were therefore not made on the same sample of blood, but A. B.'s condition was unchanged. The alteration in the blood due to travelling (apart from what may have taken place during defibrination) was not greater than the possible variations from day to day in a person whose condition was not appreciably altered.

Methods.

The methods used in the investigations have been the same as those used for ten normal cases, with one exception, namely, that the Haldane apparatus was used for the oxygen dissociation curves and not the differential apparatus. Otherwise the methods were as follows: For the hydrogen-ion concentration of the reduced blood, the hydrogen electrode as described by Parsons was used; for the CO_2 content, the differential blood-gas apparatus; for the equilibration, the

Barcroft saturator. It is not proposed here to enter into any discussion as to whether these methods are better or worse than others; our point is that they are strictly comparable for the two sets of observations—A. B. and the normals. It will be observed that the measurements of the CO_2 content were for the whole CO_2 in the reduced blood.

When the measurements which are discussed below had been made in A. B.'s blood, it became clear that the basis of knowledge concerning normal human blood was insufficient for any proper comparison to be possible. There were, of course, numerous data concerning such matters as the relation of the CO_2 pressure to the CO_2 content and of the hydrogen-ion concentration in normal blood; but these data had been acquired by different observers, by different methods, at different times, and on the blood of different individuals. It was not clear how they could be pieced together in order to give a complete and accurate picture of the relationships which exist in the blood of one normal person. In particular, it was very difficult from the data at hand to make out the extent to which the observed divergence depended upon different methods of investigation, and the extent to which they depended upon the individual eccentricities of the normal persons who were the subject of research. An investigation was therefore undertaken in the blood of ten normal adults of ages between 20 and 50 in whose blood the following relationships were determined:

1. The relation of the hydrogen-ion concentration to the pressure of carbonic acid.
2. The pressure of carbonic acid to the volume of the same (the CO_2 dissociation curve).
3. The concentration of hydrogen-ions to the volume of carbonic acid.
4. The hydrogen-ion concentration to the affinity of the blood for oxygen as measured by the value of K^n in the equation: $\frac{Y}{100} = \frac{Kx^n}{1 + Kx^n}$, where Y = percentage saturation of the blood with oxygen, x = the oxygen pressure, $n = 2.2$; K is the equilibrium constant.
5. The relation of K to the pressure of CO_2 .
6. The relation of K to the volume of CO_2 .

Of the above six relationships, the first three concern themselves principally with the plasma, the second three with the corpuscles, or more correctly with the relation of the corpuscles to their environment. When these six sets of data were worked up mathematically by A. V. Hill, it became evident that the old practice of using the logarithm of the hydrogen-ion concentration,³ rather than the hydrogen-ion concentration itself, was really a form of obscurantism which served to cloud much that was simple and beautiful in fabric formed by the interrelation of the properties of the blood. The theoretical form of the CO_2

³ The use of the actual numerical stationary concentration (cH) instead of its logarithm (pH) was recommended in the Medical Research Council Report on the acid base equilibrium of the blood, on the simple and unimpeachable ground that the symbols represent the actual qualities under discussion.

dissociation curve may be taken as an example of the simplicity of such relations—given the content of CO_2 at a stated pressure, construct the CO_2 dissociation curve. This is easily done when one takes the following facts into account:

1. For a given CO_2 content the concentration of hydrogen ions varies directly with the pressure.

2. For a given CO_2 pressure the concentration of hydrogen ions varies inversely with the CO_2 content of the blood.

The theoretical principles which govern the form of the CO_2 dissociation curve may be taken as an example of the simplicity of the relations involved. The following normal case demonstrates this:

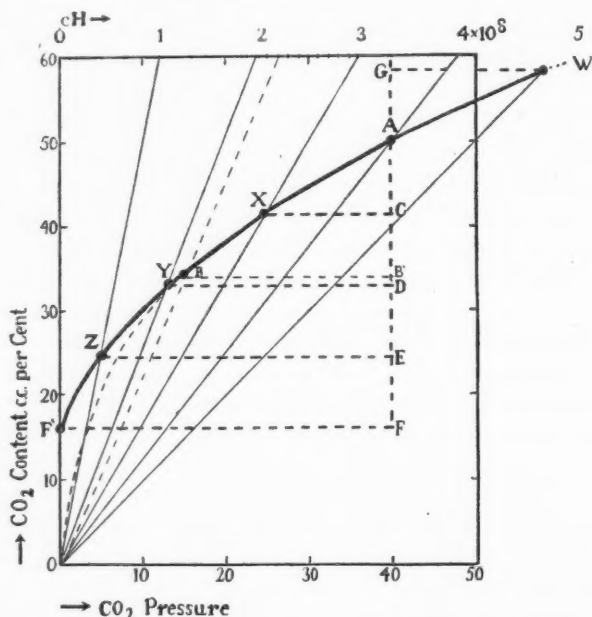


FIG. 1. Theoretical treatment of a normal CO_2 dissociation curve.

Given two points, and the hydrogen-ion concentration at one of them, construct a dissociation curve.

Let the two points be

	CO_2 pressure.	CO_2 content.	$\text{cH} \times 10^8$.
A	40	50	4
B	15	34	

Join OA and produce it to some convenient horizontal line (say that of 60 volumes per cent.) which can be used as a scale. Mark the point of intersection of OA produced which corresponds to $\text{cH} \times 10^8 = 4$, with the horizontal line as drawn. This point happens to correspond to 48 mm. pressure; therefore

along this line each 12 mm. of pressure corresponds to $\frac{1}{10^8}$ cH. This follows

from the general relation that $\text{cH} = \alpha \frac{p\text{CO}_2}{v\text{CO}_2}$. Mark the points at the pressure of 12 mm., 24 mm., 36 mm., and 60 mm. of CO_2 as cH 1, 2, 3, and 5 respectively, joining each of these points with *O*. There are now five lines of equal hydrogen-ion concentration on the paper, along any one of which the ratio of the free to the combined CO_2 is constant. It is possible to find the hydrogen-ion concentration of any point—as an example, take *B*. Draw a line *OB* and produce it to the cH scale: it cuts the scale at cH 2.2; this, therefore, is the cH of point *B*.

Now we may proceed to draw the curve. From *A* draw a straight line vertically downwards; from *B* draw a horizontal line to cut it, *B'*, and continue the vertical line to some point, *F*, which is so situated that $FB' : FA :: 2.2 : 4$, or, therefore, as $AB' : AF :: 1.8 : 4$. Now, in the volume units on the paper, *AB* is 15.3 units below *A*; therefore *F* will be $15.3 \times \frac{4.0}{1.8} = 34$. *F*, therefore, is 34 units below *A* and 16 above the base line. Draw a horizontal line through *F* to cut the ordinate at *F'*. Now divide *AF'* into four equal parts at *C*, *D*, and *E*, situated 8.5 units apart. Through *C* draw a horizontal line to meet the cH = 3 line at *X*; through *D* draw a horizontal line to meet the cH = 2 line at *Y*; through *E* draw a horizontal line to meet the cH = 1 line at *Z*. Draw a curve through *F'*, *Z*, *Y*, *X*, *A*. To produce it obtain a further point *G*, 8.5 divisions above *A*, and draw a horizontal line through *G* to cut cH = 5 at *W*.

The dissociation curve so drawn is a theoretical one, which, at all pressures but the lowest, agrees with that found by experiment, as shown by the following figures:

CO ₂ Pressure.	Volume calculated.	Observed.
10	29.8	28
20	38	38
30	44.7	44.7
40	50	50
50	54.7	54
60	59	58

At pressures below 10 mm. the observed curve departs from the calculated one, because in the presence of haemoglobin the alkali present, the amount of which is represented by *OF*, breaks up and loses its CO_2 . Whilst in practice the dissociation curve differs at low pressure from the theoretical curve as we have drawn it, this divergence tends to conceal the principal factors of which the curve is the expression. They are two in number: one is the amount of alkali present represented by *OF'*, the second is the degree of buffering represented by the interval *AC* (the amount of CO_2 taken up for each increment of 1×10^8 cH). In volumes of CO_2 , *OF'* is 16 and *AC* is 8.5. Thus, when $\text{cH} \times 10^8 = 1$, the CO_2 volume would be $16 + 8.5$, when it equals 2 the CO_2 volume would be $16 + 2 \times 8.5$, and when *N* the volume would be $16 + N \times 8.5$, or expressed in an equation it is

$$v\text{CO}_2 = 16 + 8.5 (\text{cH} \times 10^8).$$

This agrees almost exactly with that of the average of the ten cases to which allusion has already been made. It was found in three cases that

$$v\text{CO}_2 = 16.6 + 8.4 (c\text{H} \times 10^3).$$

What, then, are the normal limits of the two factors involved? Putting the equation in its general form $v\text{CO}_2 = C + B (c\text{H} \times 10^3)$, c in normal cases varied between 9 and 23, while b varied between 6.5 and 10.1. It may be well to tabulate the values for b and c in a way which was not done by the writers of the papers, namely, to start with the lowest value of b .

Case.	b .	c .
MacLean	6.5	23
Bock	6.7	27
Porter	6.9	21
Collis	7.9	19
Prestman	7.8	21
Shoji	8.1	15
Redfield	9.5	13
Barcroft	10.1	9

It will be seen that, roughly speaking, the lower the value of b , the higher the value of c . In other words, as was pointed out to us by M. L. Anson and A. E. Mirksy, in normal persons the greater the degree of buffering the less the degree of alkali present. In this way the CO_2 content at the alveolar CO_2 pressure is approximately equalized. In Barcroft's case there is independent evidence of the relation which exists between b and c , for the titratable alkalinity (c) has always proved to be low, whilst the hydrogen-ion concentration of his blood at 40 mm. CO_2 pressure is not lower than the average. The normal relation between the alkalinity and the buffering is shown in Fig. 2.

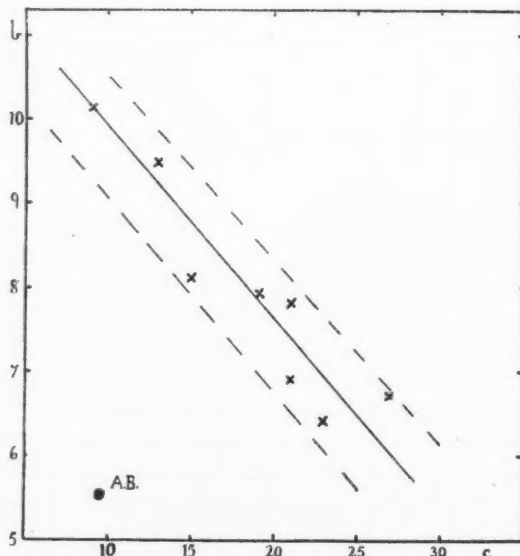


FIG. 2. Relation of alkalinity (c) to degree of buffering (b).

Properties of A. B.'s Blood.

1. *The relation of the CO_2 pressure to the CO_2 content.* We have the data for the construction of a curve such as that given in Fig. 1. The observed points are put on paper; a free-hand line is passed through them, which gives (as accurately as the observed points themselves permit) the following data:

CO_2 pressure	CO_2 volume
20 mm.	29.5 c.c. per cent.
40 mm.	39.5 c.c. per cent.
cH at 40 mm.	5.4×10^8 .

Proceeding from these data precisely as we did in the normal case, we get the following values for the alkalinity (c) and the buffering (b), respectively, $b = 5.5$, $c = 9.5$; a comparison of these figures with those of normal persons shows that neither of them is far from what might be considered normal, each being situated close to the lower limit of normality; but the combination is entirely abnormal in producing the CO_2 dissociation curve which, while it starts from the lowest point consistent with normality, rises more slowly (Fig. 3) than that of normal persons. Had we no further data we might say, then, that A. B.'s blood lacked in alkalinity and lacked in buffering in comparison with the average normal.

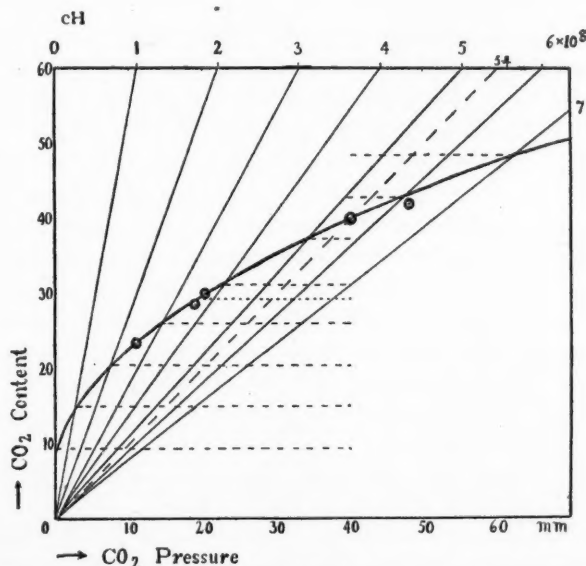


FIG. 3. Theoretical treatment of A. B.'s CO_2 dissociation curve, showing slight deficiency in alkalinity (c) and buffering (b).

Now let us see to what extent other results corroborate the above.

2. *Relation of hydrogen-ion concentration of plasma CO_2 pressure is one of those relations which is nearly linear.* The comparison of A. B. with normal

persons is given in Fig. 4. Here it is evident that at any given CO_2 pressure her blood is less alkaline than normal. In fact the hydrogen-ion concentration is approximately 50 per cent. greater in A. B.'s blood than in the normal. The average normal is expressed in Fig. 4 by the line in the middle of the shaded portion. The shading represents the range of normal.

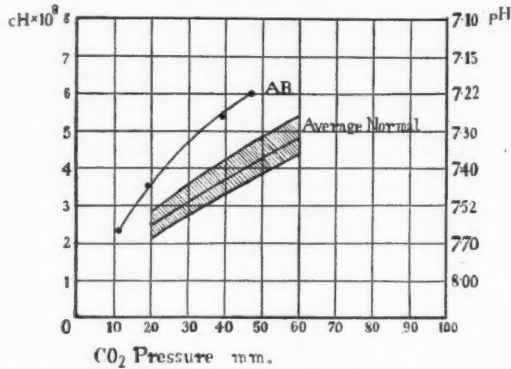


FIG. 4. The relation of hydrogen-ion concentration of plasma to CO_2 pressure in the blood of normals and of A. B.

It was found that the CO_2 pressure of A. B.'s alveolar air was 39 mm., which would indicate that her arterial blood, as it circulates in her body, must be much more acid than the most acid normal. Indeed, from Fig. 4 the cH would be estimated as 5.4×10^8 . In comparison to this, if a normal woman's alveolar CO_2 be assumed to be 37 mm. her blood would have a cH of 3.4×10^8 .

3. *The relation of the CO_2 volumes to the hydrogen-ion concentration* shown in Fig. 5 is, perhaps, the most interesting of the relationships described. In the normals it is a straight line with the equation $v\text{CO}_2 = 8.4 (\text{cH} \times 10^8) + 16.6$. This simple equation expresses two important facts about the blood, (a) the extent to which it is buffered; (b) the quantity of bicarbonate which it contains. The 8.4 signifies the number of cubic centimetres of CO_2 which must be added to 100 c.c. of blood to shift the concentration of hydrogen ion 1 gram. of ionized hydrogen litre. This is the same at all values of the CO_2 content and hydrogen-ion concentration. The constant 16.6 is a measure of the bicarbonate present; that is, if the CO_2 were shaken out of the blood till the hydrogen-ion concentration was infinitely small there would still remain 16.6 c.c. of CO_2 in combination with alkali, which could be displaced on addition of acid.

The first interesting point about A. B.'s blood is that her buffer-line is straight like the normals. This goes to show that the straightness of the buffer-line for normal blood is not accidental, but is a general property of blood, normal or otherwise. The direct determination of the constants of A. B.'s blood gives the equation $v\text{CO}_2 = 5.3 (\text{cH} \times 10^8) + 10$, which agrees very closely with the equation derived from Fig. 3.

The second point of interest is that the buffering is different and markedly

less, 5.3 c.c. of CO_2 producing the same change in reaction which requires 8.4 c.c. in normal blood. On this showing the buffering of A. B.'s blood would be but 63 per cent. of the normal. The principal buffer in blood is, of course, haemoglobin, and therefore one might expect that in A. B.'s case the haemoglobin value of the blood would be low; and this was in fact the case, though not so low as the equation would suggest. It was about 80 per cent. of the normal.

The third point of interest is the lowness of the constant, 10 as compared with 16.6 for normal blood, the bicarbonate being present in less than two-thirds the average quantity. So far the volume of CO_2 , the pressure of CO_2 , and the hydrogen-ion concentration have been taken in pairs, or ostensibly so, but all three can be expressed in the same equation, namely, $\text{cH} \times 10^8 = \alpha \frac{\text{pCO}_2}{\text{vCO}_2}$.

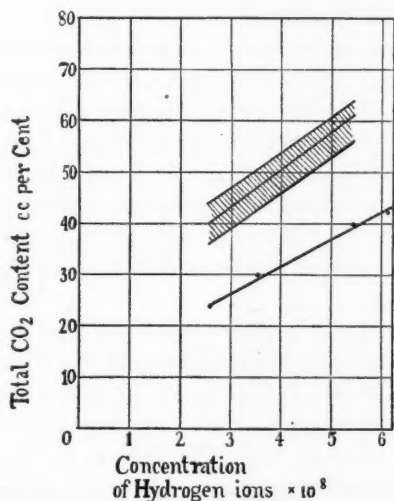


FIG. 5. The relation of the CO_2 volumes to the hydrogen-ion concentration.

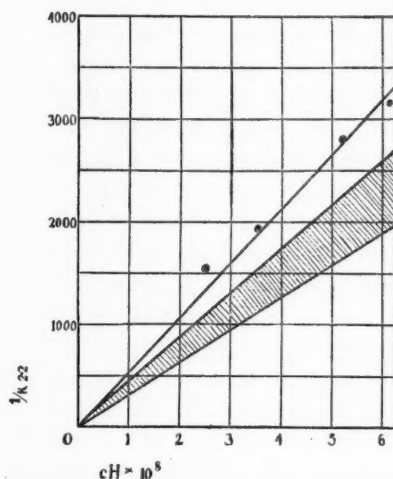


FIG. 6. The relation of $1/K$ to the cH .

This is, practically, Hasselbalch's equation. We may write $\text{cH} = x \times \frac{\text{pCO}_2}{\text{vCO}_2}$. For normal blood ' x ' is 4.7, for A. B.'s blood ' x ' is 5.4. It is rather striking that the abnormal condition of A. B.'s blood has made so little change in this constant. Miss Ruth Conway, working in Professor Hill's laboratory, found that different animals have very considerably different values for the constant ' x ', and it is quite natural that the blood from members of the same species, especially from sick people, should have at any rate small variations.

The Corpuscles.

The affinity of the haemoglobin for oxygen at 40 mm. CO_2 pressure is shown in Fig. 8, curve B, as compared with that of a normal person, curve A. In each case the curve is represented by the equation $\frac{Y}{100} = \frac{Kx^n}{1 + Kx^n}$. Y is the percentage.

saturation of the blood with oxygen, α the oxygen pressure in millimetres, and $n = 2.2$. On the physical conception, on which this theory was based, K is the equilibrium constant of the reaction; the discussion of this point will be reserved; here it need only be said that the difference between the two curves is the difference in their K 's. The following relation between K (if $n = 2.2$) and the concentration of hydrogen ion in the plasma has been shown for normal blood. If I/K be the ordinate of a graph such as Fig. 6 and cH be the abscissa, the line relating the two is a straight one which passes through the origin and may therefore be represented by the equation $I/K = \alpha \times (cH \times 10^8)$. In the case of normal blood α may vary from 316 to 436, as shown in Fig. 6. In the case of A. B.'s blood the same type of remarkably simple relation appears to exist, for if a line be drawn in which the value of α is taken as being approximately 550, the points determined appear to lie upon it within reasonable limits.

The interest of this conclusion is heightened by the following consideration. If it is a fact that the equilibrium constant of the reaction bears a simple linear relation to the hydrogen-ion concentration of the order $I/K = \alpha (cH \times 10^8)$, the fact must be true irrespective of any particular theory of the reaction. Thus Haldane, Haldane and Douglas, and also L. J. Henderson have put forward quite different theories from that of Hill, but even if none of these theories expressed the ultimate truth, the linear relationship between I/K and cH would remain, and Fig. 5 would still represent the facts as between A. B.'s blood and the normal, though the scale of the ordinate would differ.

L. J. Henderson and also Adair pointed out another relationship of I/K , namely, that if plotted against the CO_2 tension it formed a straight line over a great part of the graph. L. J. Henderson drew attention to the fact that at its extremities it must break away into a slight deflexion. This deflexion is more marked if n be taken as 2.2 than if it be taken as 2.5.⁴ Fig. 7 shows the line in question for the average normals. The points in A. B.'s blood, of which eleven are shown, fall into this scheme with extraordinary exactitude, showing that for any CO_2 pressure between 20 and 80 mm. I/K is approximately 100 per cent. greater in the case of A. B.'s blood than in the case of average normal.

Reverting to Fig. 6, the question arises, Why does the relation of the oxygen-combining power of the haemoglobin to the hydrogen-ion concentration of the plasma differ in A. B.'s blood from that of normal persons?

The crucial experiment of dividing a sample of blood into two portions, adding acid to one and not to the other, and determining the $I/K/cH$ relationship in each, has never been performed; but series of determinations, however, exist in which this relationship has been determined for the blood of a person (a) with acid added and (b) normally, the two sets of determinations (a) and (b) having been made on different occasions. In the physiological range the two sets of $I/K/cH$ points fall on lines which practically coincide, though the two lines diverge as the blood becomes more alkaline, giving the impression that the most alkaline of the 'normal' points has been erroneously determined, for it is

⁴ See Fig. 4, *Journal of Physiology*, 1922, lvi. 167.

not on any line which is consistent with the equation $I/K = \propto cH \times 10^8$. The points for the blood to which acid was added are exactly on such a line. This line is only just outside the normal range. The evidence thus, so far as it goes, is that some change in the blood has taken place further than can be imitated by the mere addition of lactic acid to shed blood.

It may be that on the addition of acid in the body the corpuscles take up more than they would do outside; that is, the living corpuscles may have a function in preventing the plasma from becoming too acid, and that this excess of acid in the corpuscles is not released when the blood is shed, though it would not be acquired by the corpuscles if the acid were added to shed blood.

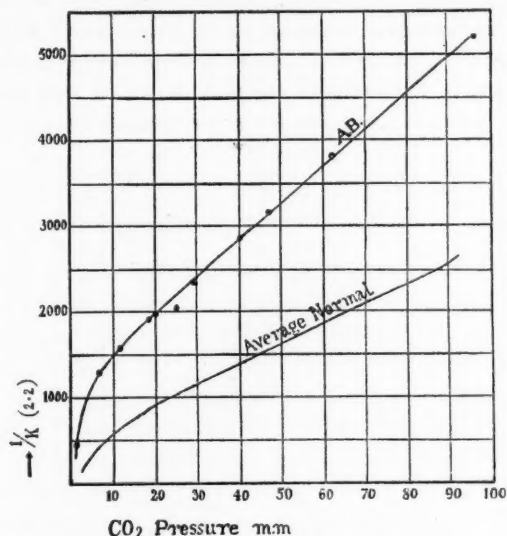


Fig. 7. Comparison of I/K with the CO_2 pressure.

It is known, of course, by the work of Milroy and that of Miss Conway, that the interior of the corpuscles is more acid than the exterior (surrounding medium). On the other hand, the exaggerated changes in I/K as compared with cH may be due (as is suggested in the paper of Barcroft, Bock, Hill, Parsons, Parsons, and Shoji (1922)) to a change in the total quantity of base present in the corpuscles, and it is shown there that a very slight deficiency or excess in this respect would produce a considerable change in the position of the line.

From the point of view of physiological function, the fact remains, whatever its cause, that the corpuscle has lost some of the oxygen content which it would have under any given conditions of oxygen pressure, because the reaction of the blood is less alkaline than that of normal blood, but partly, and in addition to that, from some other cause affecting the interior of the corpuscle.

Curve B, Fig. 8, is drawn from the equation $Y = \frac{Kx^2}{1 + Kx^n}$, where $n = 2.2$

and $K = 0.00345$, the value obtained from Fig. 6 for 40 mm. pressure. The data from which Fig. 6 was compiled were obtained at Cambridge from blood which had travelled on ice from Edinburgh. The points shown on the curve were obtained in Edinburgh on the blood drawn at the same time.

Having made the above examination of the blood, the question now arises, To what extent has any light been thrown on the problem which originally drew our attention to A. B., namely, the explanation of her cyanosis?

A. B.'s arterial blood was just 91 per cent. instead of 96 per cent. saturated with oxygen. Her oxyhaemoglobin dissociation curve at 40 mm. CO_2 was determined and is shown in Fig. 8, curve B. The calculated oxygen saturation at 40 mm. CO_2 pressure and 100 mm. oxygen pressure is 90.8 per cent. A. B.'s arterial blood was saturated about up to the point which would bring it into equilibrium with the alveolar air. There is therefore no need to assume that parts of the lung were ill ventilated, or that the blood was in any way short-circuited, or that the pulmonary alveoli or vessels were impermeable.

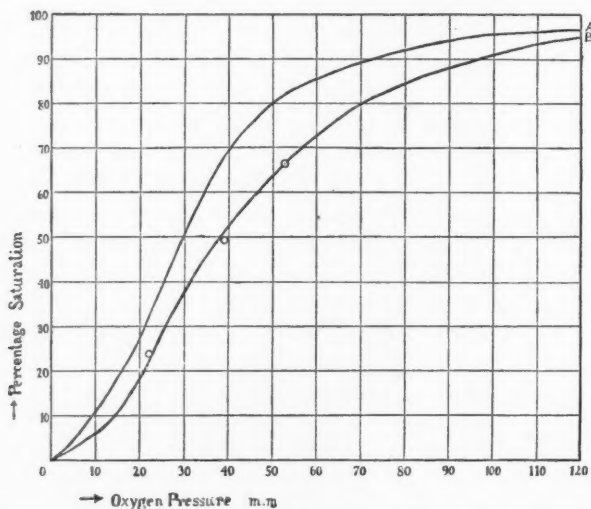


FIG. 8. B = oxygen dissociation curve of A. B.'s blood at 40 mm. CO_2 pressure; A = normal.

It seems evident that, given the usual circulation rate as a maximum (and there is no reason to believe that it was accelerated), her venous blood must have been much less saturated than is ordinary venous blood. This would be so even if the oxygen dissociation curve of the venous blood were no lower than that given for 40 mm. pressure of CO_2 . If the oxygen pressure in A. B.'s mixed venous blood were 35 mm. the saturation could be under 50 per cent. The colour of the skin follows the saturation of the venous blood rather than that of the arterial, but on any theory of cyanosis the capillary blood in A. B. would be unusually dark (see Fig. 8). Fig. 9 shows the oxygen dissociation curve of the second case at 33 mm. CO_2 pressure; the value of K for it is only a trifle

lower than lowest values found in the circulating blood of normal persons. The average normal blood would necessitate a pressure of 45 mm. instead of 33 mm. to produce a like change in the dissociation curve. Probably here also the inside of the corpuscle is more acid than is normally the case at any specified CO_2 pressure.

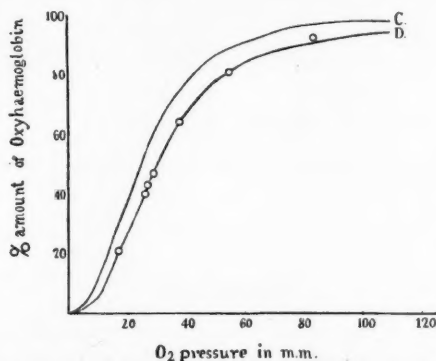


FIG. 9. D = oxygen dissociation curve of F. R.'s blood at 33 mm. CO_2 pressure; c = normal.

Though there is little difficulty in accounting, at all events partially, for A. B.'s and F. R.'s colour, there still remains to be discussed the colour of their blood when shed—for this, when shaken up with air, had not the brilliant hue of normal human blood. The presence of an abnormal pigment, in the form of sulph-haemoglobin, was demonstrated in the blood in both cases. Although this probably gave to the shed blood the peculiar greenish-yellow tint already noted, it does not seem possible that this would altogether account for the change in colour. In this connexion it may be worth noting that the oxygenated blood, though dull in colour—judged by the standards of human blood—did not differ greatly in appearance from ox blood. This fact suggests that the cause of the abnormal colour had to do with the refrangibility of the corpuscles rather than with the nature of the pigment which they contain. It is known that the addition of CO_2 (and other acids) swells up the corpuscles, and also that some changes in the relation of intracorpuseular salt content to that of the plasma may produce a similar result.

Work on the first case described above was commenced in 1920, and therefore most of the determinations described in this paper were carried out before the publication of investigations of the blood on parallel lines in Professor van Slyke's laboratory. That work differs largely from ours in that it takes the pH, not the cH of the blood as a basis of calculation. If we omit to allude to it at every point, it is not because we yield to others in the appreciation of its beauty, but because once for all we assume that it is in the hands of our readers.

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THE FUNCTIONAL PATHOLOGY OF NEPHRITIS¹

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Introduction.

THE work described in this paper has the object of correlating the symptoms of nephritis, and of finding, if possible, an explanation of their causes consistent with what is known of the physiology of the kidney. Before discussing the changes which occur, it is therefore necessary to refer briefly to some recent advances in our knowledge of the normal kidney.

The glomeruli. The study of capillary circulation in general, and the work in Richards's laboratory on the kidney of the frog, leave little doubt that the glomeruli act only as filters, impermeable to the proteins of the plasma, but permeable to all the non-colloidal constituents. Wearn and Richards (1) have demonstrated the existence of glucose in the glomerular filtrate when none was present in the urine; and the absence of protein, except when the glomerular circulation was much retarded. Wearn, Schmidt, and Richards (2) found, by direct analysis of the filtrate, a concentration of chloride nearly corresponding to its concentration in the plasma. Urea was also recognized, but could not be measured so accurately. There was rather more chloride in the filtrate than in the plasma, but this seems to be characteristic of a number of capillary exudations in the body (e.g. aqueous humour, cerebro-spinal fluid), and may perhaps be explained by the Donnan membrane equilibrium. The evidence supports the belief that glomerular filtration is a physical process, requiring only the small amount of energy necessary to separate water from a protein solution and overcome the resistance of the filtering membrane. As Starling (3) has pointed out, this energy is supplied by the blood-pressure in the glomerular capillaries.

The tubules. The urine is concentrated while passing through the tubules, and it is there that the physical work of the kidney is performed; but there is still uncertainty as to the nature of the process. The discovery of glucose in the glomerular filtrate when none was contained in the urine (1) shows that the renal epithelium can absorb glucose from the lumen of the tubules. This necessarily involves absorption of water, which doubtless accounts, in part at least, for the concentration of the urine. Cushny (4) believes that the only function which

¹ Received Nov. 27, 1925.

need be postulated for the tubule cells, in order to explain the formation of urine, consists in absorption of a fluid of constant composition—a sort of Ringer-Locke solution which he calls 'optimal fluid'. An excess of water or of any diffusible substances in the plasma entails a similar excess in the glomerular filtrate; this fraction remains unabsorbed by the tubule cells and becomes the urine, while the rest of the filtrate is returned to the blood as optimal fluid. Since only the excess is excreted, a diffusible substance existing below a certain concentration in the plasma may be absent from the urine. The critical plasma level is called the 'threshold' of excretion, and such a substance is termed a threshold body. Sodium chloride and glucose belong to this class; the former is usually a little above its threshold level in the plasma, while the latter is normally kept well below its threshold by oxidation in the tissues. In the case of other constituents, which may more properly be regarded as waste products, the existence of a threshold level has not been established, and these are termed 'no-threshold' bodies. The no-threshold class includes urea, sulphate, and other substances; but recent evidence seems to necessitate the assumption of a low threshold for some of these, and perhaps for all.

The possibility of secretion has not been excluded, however. Numerous physiologists believe that the tubule cells can secrete, although most admit the absorption of chloride and glucose. Starling and Verney (5), dealing with excretion by kidneys perfused with oxygenated blood, which has circulated also through the heart and lungs, find that the addition of a very small amount of cyanide to the blood causes a temporary reduction in the output of urea, while the output of chloride and the volume of urine are increased; and they conclude that urea-secreting and chloride-absorbing cells must have been poisoned. But it seems equally probable that urea diffuses from the tubules into the injured cells, during their effort to concentrate the urine by absorption of water. The difficulty of interpreting the results of interference with the function of the tubules is apparent when we consider that, whatever the mechanism of this function might be, its gradual suspension would probably lead to excretion of urine more and more closely resembling glomerular filtrate.

Nephritis.

Since filtration and concentration are distinct phases in the production of urine, it seems desirable, for the purpose of this paper, to adopt a classification of nephritis which separates, as far as possible, diseases affecting these two functions of the kidney. While it is useless to suggest that any disease attacks one function exclusively, it will be shown that MacLean's (6) division into hydraemic and azotaemic types is, broadly speaking, a distinction between impairment of filtration and loss of concentrating power. This classification is therefore more suitable than those which rest on a histological basis. The two varieties are fundamentally distinct, although hydraemic nephritis, in its more advanced stages, may become azotaemic. The usual form of acute nephritis

resembles more closely the hydraemic type, and may pass into it if recovery is not fairly rapid. There is no need to defend the statement that in azotaemic (chronic interstitial) nephritis the concentrating function of the kidneys is impaired, and, since in typical cases there is no evidence, other than histological, of serious interference with filtration, further discussion may be postponed until this disease is considered in detail. As regards hydraemic (chronic parenchymatous) nephritis, renal function tests prove the concentrating power to be normal for urea, and it will be shown later that chloride retention is not necessarily due to disease of the tubules, or may indicate comparatively slight damage; hence our conception of the functional changes in the kidney must depend chiefly on the route by which protein reaches the urine. This protein is derived from the plasma without alteration, so far as is known, except in the relative proportions of albumin and globulin. It is probable that most or all passes through the glomeruli, since certain foreign proteins, when injected into animals, have been shown to do so (7); and the condition of functional albuminuria is best explained by this supposition. Hence hydraemic nephritis may be regarded as a disease mainly involving filtration; the glomeruli having become permeable to protein, while the function of the tubule cells is less affected. This view seems inconsistent with the microscopic changes found in the kidney. The glomeruli may appear little altered, while the tubule epithelium shows cloudy swelling, fatty degeneration, and often more serious impairment. It is not necessary to suppose that permeability to protein must imply a recognizable change in the glomeruli, since normal capillaries in some parts of the body may not be quite impermeable; the appearance of the tubules, however, cannot easily be reconciled with the condition of renal function. But, in spite of structural alterations, physiologists can scarcely avoid the conclusion that the renal epithelium retains most of its functional efficiency. For, whether the tubule cells are assumed to secrete or to absorb, no one doubts that the chief part of the physical work of the kidney is done by these cells. And since in pure hydraemic nephritis urea is concentrated effectively, and kept about the normal level in the plasma, it cannot be supposed that this work is much reduced; while a lower content of chloride in the urine than in the plasma also entails the expenditure of energy by the kidney.

Hydraemic (Chronic Parenchymatous) Nephritis.

The characteristic features of this disease are excessive albuminuria, oedema, slight or considerable reduction in the volume of urine, and retention of chloride; but efficient excretion of no-threshold substances (e. g. urea), in so far as the output of urine permits. These changes will be considered in turn, in order to determine how they are related to one another, and whether any interdependence can be discovered.

Albuminuria. The presence of protein and occasionally blood corpuscles in the urine of acute nephritis suggests that the glomerular filtrate has assumed some characteristics of an inflammatory exudation; and it is natural to suppose

that this kind of albuminuria results from an inflammation of the glomerular tufts, which may later become chronic. In recent years, however, there has been a tendency to regard the disease as more general: affecting not only the kidney but also the tissues concerned in the formation of plasma. It is conceivable that, owing to some defect in the kidneys or in the plasma-forming tissues, the serum proteins are being treated as foreign bodies. The continued excretion of protein might produce further changes in the kidney. The question will be discussed more fully at a later stage.

Oedema. The oedema of nephritis has been believed to result from hydraemia caused by failure of the kidneys to eliminate water; but recent workers have been unable to observe any increase in plasma volume, and sometimes an actual decrease has been found to occur. The proportion of corpuscles to plasma may be abnormally high, especially in acute cases; when the disease is chronic, however, a negligible change in the opposite direction is more usual. The water-holding power of proteins has also been considered in relation to oedema. Martin Fischer (8) suggested an increase in the power of imbibition possessed by the tissue proteins, owing to local formation of acid. But no sufficient change of reaction could occur during life; and, in any case, subcutaneous oedema has no relation to the swelling of gelatin, for fluid is free in the tissues and can escape through punctures in the skin. Another theory depends on the important observation by Starling (3) that the proteins of the plasma have a definite water-retaining power or osmotic pressure. Starling found that normal plasma, contained in tubes of animal membrane, could hold water against a pressure of about 30 mm. of mercury. This property of the plasma proteins tends to prevent fluid being forced into the tissues by the capillary blood-pressure. Epstein (9) suggested that a fall in the protein osmotic pressure of the plasma is the cause of nephritic oedema. Later investigation has tended to support this hypothesis, although it has been criticized by various subsequent writers. MacLean and de Wesselow (10) base their criticism on the fact that oedema may disappear without an increase in the total protein of the plasma, but fail to differentiate between albumin and globulin. In a recent paper by Linder, Lundsgaarde, and Van Slyke (11), it is objected that the plasma proteins may be greatly reduced without the onset of oedema, and that absorption and reappearance of the exudate cannot always be correlated with changes in the albumin and globulin content of the plasma; the experiments did not include actual measurements of the water-retaining power. But Krogh (12) has pointed out that the normal protein osmotic pressure of the plasma is much higher than the capillary blood-pressure, and that a very substantial diminution must take place before oedema can occur. An additional factor complicates the problem, for if the patient improves and fluid is absorbed, that which is left must gradually tend to regain the protein concentration of normal lymph; and, since the colloid osmotic pressure of this fluid opposes that of the plasma, the process of absorption is likely to become slower in its final stages. In view of the doubtful value of current criticisms we may assume that the chief cause of nephritic oedema is failure of the plasma proteins

to retain water in the circulation, and that exudation of fluid at points of higher capillary pressure can no longer be balanced by absorption at neighbouring points where the pressure is lower. Absorption by lymphatics is probably too slow to deal with a large excess of fluid.

Moore and Parker (13) have invoked the protein content of normal lymph as an objection to Starling's theory of lymph balance, and this objection cannot be altogether disregarded. The effect, however, is merely to reduce, not to abolish, the force which the plasma proteins exert. And when oedema occurs, perhaps even before it can be recognized clinically, the protein in the tissue fluid is so much diluted that its osmotic pressure need no longer be considered.

The colloid osmotic pressure of the plasma appears to be exerted chiefly by serum albumin; globulin and fibrinogen taking but little part, possibly because their molecules are larger and therefore fewer for a given weight of protein. Any form of albuminuria involves a loss of plasma proteins, and the colloid osmotic pressure of the plasma is reduced. But in many diseases without either albuminuria or oedema a moderate reduction may be observed. *Hydraemic nephritis* is characterized in severe cases by a particularly low colloid osmotic pressure of the plasma, unapproached in any other condition as yet examined, and apparently the sole cause of the oedema in this disease. In a case described by Hagedorn, Rasmussen, and Rehberg (12), working in Krogh's laboratory, the serum contained 5 per cent. of protein and had a colloid osmotic pressure of less than quarter the normal value. The urine, although containing less protein than the plasma, had a higher colloid osmotic pressure; and it is suggested that the glomeruli were more permeable to the small and osmotically active protein molecules than to the larger and less active. Recent papers by Govaerts (14), by Schade and Claussen (15), and by Rusznyák (16) also emphasize the importance of low plasma protein osmotic pressure in the causation of nephritic oedema. In addition to the analyses of plasma protein given by Linder, Lundsgaarde, and Van Slyke (11), similar work has been published by Kollert and Starlinger (17), and also by Rowe (18) and other less recent observers. There is fairly general agreement that in *hydraemic nephritis* fibrinogen and globulin are much less reduced than albumin; and this gives some support to Krogh's suggestion.

If the above theory of nephritic oedema is correct, it should be possible to distinguish *hydraemic nephritis* from other diseases by examination of the plasma proteins. The oedema of cardiac failure should occur at a higher level of colloid osmotic pressure, because the capillary blood-pressure is higher. Oedema due to increased permeability of the capillary endothelium (e.g. inflammatory oedema) should be less dependent on the condition of the plasma proteins, since the proteins would have less difficulty in leaving the capillaries, and therefore less opportunity of exerting osmotic pressure. And finally, in all diseases unaccompanied by circulatory failure or oedema, we should find that the protein osmotic pressure of the plasma is never below a certain level, provided that we can assume the average capillary blood-pressure to remain approximately normal in pathological conditions which do not directly involve the circulation.

The experiments undertaken to study these criteria were designed to be as simple as possible, in order that if the tests should prove to be of value in diagnosis or prognosis they might be employed as a routine clinical procedure. Collodion sacs of 3-5 c.c. capacity are made in centrifuge tubes by a method mentioned in a previous paper (19); using a solution (about 10 per cent.) of Sehering's celloidin in equal parts of absolute alcohol and ether. Into the necks of these sacs are inserted short pieces (about $\frac{3}{4}$ in.) of red rubber pressure tubing, which should fit as accurately as possible. The tubing is tied in by lapping tightly with cotton thread. It is convenient to have about $\frac{1}{4}$ in. of glass tube inside the lower end of the rubber tubing and flush with its under surface,

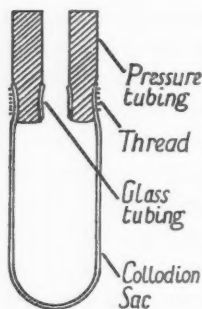


FIG. 1.

in order to resist the pressure of the thread. A stock of sacs prepared in this way is kept in water, and each may be used a considerable number of times. When a sample of plasma is to be examined a sac is emptied of water as thoroughly as possible by shaking, washed out once or twice with a few drops of the plasma, and then, by means of a nipple pipette, completely filled to the top of the rubber tube. All air-bubbles are induced to come to the surface and removed. A thick-walled capillary-bore glass tube (e.g. 0.8 mm. barometer tubing) about 50 cm. in length is then introduced, until it is felt grating against the short glass tube already mentioned. In this process the plasma in the rubber tubing is displaced, and rushes up the capillary. The level reached depends, of course, on the bore and length of the rubber tubing, which should be such that the height attained is not very different from the expected osmotic pressure. The collodion sac is now completely immersed in about 50 c.c. of Ringer solution contained in a small beaker, and the apparatus is supported by clamping the upper end of the barometer tube in a stand which retains it in a vertical position. The crystalloids of the plasma and Ringer solution can diffuse freely through the wall of the sac, and when equilibrium is established the height of the column of plasma above the surface of the outside fluid represents the colloid osmotic pressure or water-holding power of the plasma proteins plus the capillary value of the barometer tube for the plasma. The measurement is made after eighteen to twenty-four hours, and the temperature of the room should be fairly constant for a couple of hours before the reading is taken. A correction for capillarity (which depends chiefly on the bore of the capillary and the surface tension of the plasma) is then made by squeezing the plasma from the sac into a small dry beaker, dipping in the end of the barometer tube, noting, after two or three minutes, the height to which the plasma has risen, and subtracting this from the original reading. The colloid osmotic pressure is thus obtained in centimetres of plasma, and can, if desired, be expressed in centimetres of water or millimetres of mercury, by making a correction for the specific gravity of the plasma. This, however, is unnecessary, for we wish to determine not the absolute osmotic pressure but the relation of the osmotic

pressure in disease to that of normal plasma; and the method contains greater sources of error than could be introduced by differences in the specific gravities of various samples. For the same reasons it was considered unnecessary to conduct the experiments at blood heat, which would have the disadvantage of rendering changes in the proteins more rapid; and the lower temperature probably accounts for slightly lower results in the case of normal plasma than those which Krogh has obtained at 37° C. (12). Stretching of the collodion membrane might be a possible cause of error, but the pressure reached does not seem high enough to cause appreciable distension of the small, rather thick-walled sacs which were employed; and, in any case, the stretching after eighteen hours would have become so slow that it would probably be compensated as rapidly as it could occur. Larger unsupported sacs have been used both by Lillie (20) and by Loeb (21), in whose work considerable accuracy was required, and neither appears to have observed any error from this cause. The criticism of Sørensen's (22) more rapid and complex technique with regard to this point apparently loses much of its force when applied to the slower method. It should be emphasized that the barometer tube used must be of narrow bore, for otherwise an appreciable amount of water would have to enter or leave the sac before the pressure could rise or fall to the point of equilibrium; and the resulting change in concentration of the proteins would affect the ultimate reading. There seems to be no objection to keeping the plasma in a refrigerator for forty-eight hours before making the determination, but this has only occasionally been necessary.

The question must be considered of the effect of reaction and salt concentration on protein osmotic pressure. The work of Lillie (20), Loeb (21), Sørensen (22), Pauli (23), and others leaves no doubt that the addition of small amounts of acid or alkali to pure solutions of proteins causes a great increase in their osmotic pressure, which is lowest at their iso-electric point. The proteins can act as acids or bases, and the salts formed in either case have a higher osmotic pressure than the protein; owing, presumably, to the attachment of one or more inorganic ions to each molecule and the formation of a dissociable compound. The presence of neutral salts tends to reduce the osmotic pressure of proteins, perhaps by encouraging aggregation (Lillie), or by resulting in an unequal distribution of diffusible ions on the two sides of the membrane (Bayliss). But it seems that in experiments on plasma these effects may be ignored. The serum proteins at the normal reaction of the blood are acting chiefly as acids, and are united to inorganic basic ions. At a more alkaline reaction all their acidic affinities would be satisfied, and they should then attain their highest osmotic pressure for an alkaline medium. There would be another maximum for an acid medium with the protein acting as base. Yet it is found that in Ringer solution made strongly alkaline to phenolphthalein the colloid osmotic pressure of normal plasma does not differ appreciably from that in ordinary Ringer solution. As regards salt concentration, it is found in this case also that considerable changes have practically no effect on colloid osmotic pressure, possibly because the salt content of the plasma is already so high. (It may be pointed out, in passing, that this

does not support the view that chloride retention is of importance in the causation of oedema.) It is perhaps advisable to avoid the use of oxalate as an anti-coagulant, for if this substance is employed the colloid osmotic pressure may be altered by replacement of calcium ions attached to the proteins. Heparin (Howell (24)), in the proportion of 1 mg. to 2 c.c. of blood, has been used instead throughout these experiments.

But, although its source has not been discovered, there appears to be an error of about 1 per cent. to 5 per cent. in the estimation. The pressure is often definitely lower after forty-eight hours than after twenty-four hours, and the fall tends to continue at a decreasing rate. It is therefore an arbitrary matter to decide when to take the reading, but if this is done after eighteen hours the subsequent changes are small enough to be ignored. Krogh (12) mentions the same difficulty in his experiments. The delayed fall in osmotic pressure observed by Moore and Roaf (25) in the case of previously heated gelatine suggests that the slow decrease which occurs, when the protein osmotic pressure of plasma from warm-blooded animals is measured at room temperature, may have a similar cause. But Krogh's determinations were made at 37° C. The fall is much more obvious in the case of albuminous urine than of plasma, and may be due to the presence of slowly diffusible semi-colloids.

After the measurement of colloid osmotic pressure the same plasma is used for an estimation of protein nitrogen. Since almost all the diffusible nitrogenous material has dialysed into the Ringer solution, a direct Kjeldahl determination gives nearly accurate results. The relative amounts of different plasma proteins were not estimated; but it was possible to determine indirectly whether a reduction in osmotic pressure was due solely to dilution, or whether, in addition, less osmotically active forms of protein (e.g. fibrinogen and globulin) were present in abnormal proportions. This was done by comparison with normal plasma diluted to an equal protein content.

Turning now to the results obtained, it is necessary first to substantiate the statement made with regard to the negligible effects of considerable changes in reaction and salt concentration on the colloid osmotic pressure of the plasma, measured in the manner described.

The slight differences, shown in Table I, which may occur when the colloid osmotic pressure of unaltered or diluted plasma is measured with external fluids of various reactions and concentrations do not seem to conform to any definite principle, and are probably due to error. Unless precautions are taken to avoid loss of CO₂ higher concentrations of NaHCO₃ than M/100 tend to precipitate calcium, and might thus affect the result. This table shows that greater variations in the composition of the external fluid than could occur in different experiments of a series are unlikely to introduce any serious fallacy. Other controls gave similar results.

The second and third tables show the effect of dilution on the colloid osmotic pressure of normal plasma.

TABLE I. *Mixed normal blood from healthy men. Plasma separated and dilutions with Ringer solution made as stated below. The figures represent colloid osmotic pressure in centimetres of plasma.*

Plasma.	External Fluid.				
	Sherrington's Ringer Solution.	Ditto with M/100 NaHCO ₃ .	Ditto with no NaHCO ₃ .	Ditto with Double Concentration of all Salts except NaHCO ₃ .	Ditto with Half Concentration of all Salts except NaHCO ₃ .
100 %	40.2	39.3	38.1	39.8	41.6
70 %	24.7	24.4	23.1	24.5	24.1
40 %	11.8	11.6	12.0	11.9	12.0
20 %	4.8	4.7	5.2	4.9	4.5

Indicator.	Reaction of External Fluid at end of Expt.		
Methyl red	Alkaline	Alkaline	Alkaline
Litmus	"	"	Very faintly alkaline
Phenolphthalein	Acid	"	Acid

TABLE II. *Mixed Blood from several Normal Individuals.*

Dilution of Plasma.	Colloid Osm. Pressure (cm. of Plasma).	Protein Nitrogen (gm. %).	Protein, gm. % (= protein N \times 6.25).	Osm. Pressure per gm. of Protein (cm. of Plasma).
Undiluted plasma	40.2	1.2600	7.8750	5.10
90 %	34.8	1.1340	7.0875	4.91
80 %	27.6*	1.0080	6.3000	4.88
70 %	24.7	0.8820	5.5125	4.48
60 %	20.2	0.7560	4.7250	4.28
50 %	15.7	0.6300	3.9375	3.99
40 %	11.8	0.5040	3.1500	3.75
30 %	7.8	0.3780	2.3625	3.30
20 %	4.8	0.2520	1.5750	3.05
10 %	2.4	0.1260	0.7875	3.05

* Should be about 29.0, which would give 4.60 cm. per gm. of protein.

TABLE III. *Blood from one Individual.*

Dilution of Plasma.	Colloid Osm. Pressure (cm. of Plasma).	Protein Nitrogen (gm. %).	Protein, gm. % (= protein N \times 6.25).	Osm. Pressure per gm. of Protein (cm. of Plasma).
Undiluted plasma	40.1	1.3000	8.1250	4.94
70 %	22.9	0.9100	5.6875	4.03
50 %	14.6	0.6500	4.0625	3.59
40 %	11.2	0.5200	3.2500	3.45
30 %	8.1	0.3900	2.4375	3.32
20 %	5.0	0.2600	1.6250	3.08
10 %	2.4	0.1300	0.8125	2.95

It will be seen that the osmotic pressure per gm. of protein falls considerably as the concentration of protein is reduced. (This means that if normal plasma, shown in Table II to have an osmotic pressure of about 5 cm. per gm. of protein, were to be diluted to a protein concentration of 1 gm. per cent., the

solution would then show an actual osmotic pressure of about 3 cm. (see table), not 5 cm. as calculated. An unavoidable change seems to occur on dilution. In the discussion which follows, the term 'unit osmotic pressure' will be substituted for 'osmotic pressure per grm. of protein.') Hence the plasma proteins in disease cannot be regarded as abnormal in character simply because they do not show as high a unit osmotic pressure as those of undiluted normal plasma. This might be due to a reduction in quantity alone. In order to demonstrate abnormalities other than simple dilution, a graph has been made by plotting the colloid osmotic pressures shown in Table II against the corresponding concentrations of protein, and plotting on the same chart similar data with regard to undiluted plasma in

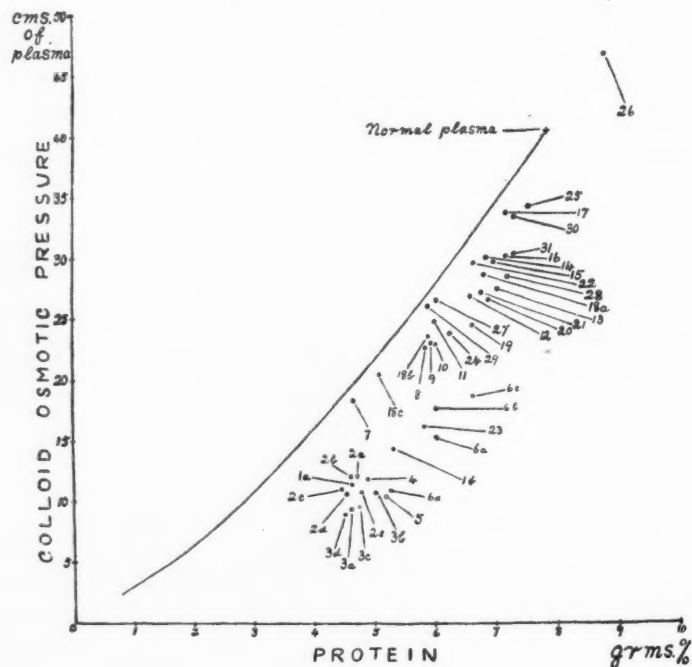


FIG. 2.

various diseases (Fig. 2). When the points obtained from the latter do not lie on or near the graph, the plasma proteins are abnormal either in character or in relative proportions. Graphs of this kind, obtained from plasmas which may be regarded as normal, are similar in type but may differ slightly in level; for there is some latitude in the plasma protein content and colloid osmotic pressure of normal individuals. In the study of disease it is, therefore, inadvisable to lay much stress on small deviations from the graph, especially when the protein content is not greatly reduced. The points on the chart are numbered to correspond with the cases, of which details are given in Table IV. Letters following the numbers denote a series of observations on the same patient.

TABLE IV.

Number.	Nature of Case.	Oedema.	Colloid Osm. Pressure (cm. of Plasma).	Protein Nitrogen (grm. %).	Protein, grm. % (= protein N x 6.25).	Osm. Pressure per grm. of Protein (cm. of Plasma).
1a. (30.7.24)	Hydraemic nephritis	Present (with ascites)	11.4	0.7420	4.6375	2.46
1b. (22.9.24)	—	—	14.3	0.8512	5.3200	2.69
2a. (7.3.24)	Hydraemic nephritis	—	12.1	0.7560	4.7250	2.56
2b. (5.5.25)	—	—	12.0	0.7384	4.6150	2.60
2c. (18.6.25)	—	—	11.0	0.7140	4.4625	2.46
2d. (2.7.25)	—	—	10.6	0.7280	4.5500	2.33
2e. (6.7.25)	—	—	10.8	0.7677	4.7981	2.25
3a. (16.6.25)	Hydraemic nephritis	Present	9.4	0.7420	4.6375	2.03
3b. (30.6.25)	—	—	10.7	0.8050	5.0312	2.13
3c. (2.7.25)	—	—	9.6	0.7630	4.7687	2.01
3d. (13.7.25)	—	—	8.9	0.7233	4.5206	1.97
4.	Hydraemic nephritis	—	11.8	0.7840	4.9000	2.41
5.	—	Slight	10.4	0.8307	5.1919	2.00
6a. (24.3.25)	Acute nephritis	Present	15.1	0.9612	6.0075	2.51
6b. (27.4.25)	—	Slight	17.6	0.9612	6.0075	2.93
6c. (25.5.25)	—	Slightly increased	18.6	1.0605	6.6281	2.81
6d. (2.6.25)	—	Much increased	10.8	0.8445	5.2781	2.05
7.	Acute nephritis	Undergoing absorption	18.3	0.7468	4.6675	3.92
8.	—	—	22.5	0.9380	5.8625	3.84
9.	—	—	22.9	0.9520	5.9500	3.85
10.	—	—	22.8	0.9612	6.0075	3.80
11.	—	Absorbed	24.7	0.9604	6.0025	4.11
12.	—	—	26.7	1.0548	6.5925	4.05
13.	—	—	27.3	1.1253	7.0331	3.88
14.	—	—	29.9	1.0973	6.8581	4.36
15.	—	—	29.6	1.1172	6.9825	4.24
16.	Azotaemic nephritis	Absent	30.0	1.1508	7.1925	4.17
17.	—	—	33.5	1.1508	7.1925	4.66
18a. (30.3.25)	—	—	28.5	1.0892	6.8075	4.19
18b. (21.4.25)	—	—	23.5	0.9472	5.9200	3.97
18c. (13.5.25)	—	Cardiac oedema	20.3	0.8154	5.0962	3.98
19.	Azotaemic nephritis	—	24.4	1.0592	6.6200	3.69
20.	Cardiac failure	—	26.4	1.1025	6.8906	3.83
21.	—	—	27.0	1.0850	6.7812	3.98
22.	—	—	29.5	1.0640	6.6500	4.44
23.	Syphilis—heart and kidneys	Ascites	16.2	0.9352	5.8450	2.77
24.	—	Anasarca and ascites	23.7	1.0010	6.2562	3.79
25.	High blood pressure	Absent	34.0	1.2110	7.5687	4.49
26.	(with cerebral haemorrhage)	—	46.3	1.4084	8.8025	5.26
27.	Pernicious anaemia	—	26.4	0.9660	6.0375	4.37
28.	Polycythemia	—	28.4	1.1527	7.2044	3.94
29.	Lymphatic leukaemia	—	25.9	0.9450	5.9062	4.39
30.	Asthma	—	33.2	1.1732	7.3325	4.53
31.	Exophthalmic goitre	—	30.2	1.1718	7.3237	4.12

Very little comment is necessary, but attention will be directed to a few of the more important results. The most striking feature is the extraordinary reduction of colloid osmotic pressure in hydraemic nephritis. In the five uncomplicated cases examined this property has not much more than a quarter of its normal value; and the figures confirm those given by other observers. The plasma has more than half the normal protein content, and thus the unit osmotic pressure is much lower than that of normal plasma. It is also considerably less than that of equally diluted plasma from a normal person; the points shown on the chart are far below the corresponding points on the graph, and hence some change in the character or relative proportions of the proteins must have occurred. In none of the cases of hydraemic nephritis did the unit osmotic pressure reach 3 cm. of plasma. These patients differed considerably in the amount of their oedema, but its persistent character formed a connecting link throughout the group. It will be noticed that in one case (No. 1) some increase in the colloid osmotic pressure took place, but the level reached was not sufficiently high to admit of disappearance of the oedema. Among the cases of acute nephritis one (No. 6) was distinguished from the rest by an unusually low colloid osmotic pressure when first examined, and a great deviation from the normal graph. There was considerable oedema at this time, with a small output of highly albuminous urine; but clinical examination elicited no exceptional features. On account of the serious change in the plasma a bad prognosis was given, and this was justified by the subsequent course. An initial slow improvement was interrupted by numerous relapses, and the disease ultimately became indistinguishable from hydraemic nephritis. There is some hope that examination of the plasma may in future enable us to give an earlier and more reliable prognosis in acute nephritis than has hitherto been possible. In another case (No. 7) the colloid osmotic pressure was comparatively low, but this was due to a low protein content of the plasma, without other alteration. The patient had been very oedematous, but considerable improvement had already occurred before the plasma was examined, and this improvement continued until the oedema disappeared. The remaining cases of acute nephritis were of fairly short duration, and were available for observation only while oedema was diminishing, although the actual amount of oedema still present was sometimes considerable. In harmony with this the plasma colloid osmotic pressure was relatively high. It is probable that in favourable cases the unit osmotic pressure is not much less than 3.5 cm. of plasma. Nephritic oedema appears to undergo absorption when the colloid osmotic pressure reaches 18 or 20 cm. of plasma. There is probably some variation with changes in capillary pressure, but in no case as yet examined has persistent renal oedema been observed with the colloid osmotic pressure above 20 cm. This pressure is somewhat lower than the apparent blood-pressure in skin capillaries, as given by recent measurements (26); but in these measurements the resistance of overlying tissues is added to the actual capillary blood-pressure, and thus the results obtained are presumably too high. Azotaemic nephritis presents no features of special interest in this connexion. The proteins are often

moderately reduced, but not sufficiently to permit of oedema unless cardiac failure occurs. The unit osmotic pressure is slightly decreased, probably by a relatively greater reduction in albumin than in globulin. In cardiac failure, also, the plasma proteins are rather low, and in this case oedema occurs at a higher level of colloid osmotic pressure. This appears to be due to higher capillary blood-pressure resulting from partial venous stasis (for the venous pressure is increased in cardiac failure (27)), and perhaps also to ill-nourished capillary endothelium. The oedema which occasionally complicates the later stages of azotaemic nephritis seems to be cardiac in origin: the degree of heart failure necessary for the occurrence of oedema depending on the amount of protein in the plasma. A case of asthma was examined because of the exudative character of the local inflammatory reactions to numerous substances injected. This transient oedema was not associated with a low colloid osmotic pressure: an observation which is consistent with the high protein content of inflammatory exudates. The only case in which the colloid osmotic pressure of the plasma was found to be above normal was one of high blood-pressure with cerebral haemorrhage (No. 26). The proteins were increased in amount, and it will be seen that the point for this case lies on an extension of the normal graph; thus indicating that the change is in concentration only. The high blood-pressure may have been caused by retention in the vessels of fluid which would normally have reached the tissues or been excreted in the urine, and may depend on the water-holding power of the excess of protein. A high colloid osmotic pressure of the plasma is not characteristic of all forms of high arterial pressure, and does not seem to occur in that associated with azotaemic nephritis. But until more evidence has been obtained of co-existing changes in capillary pressure, we can scarcely hope that any definite relations will be established. It may be possible, however, to distinguish more clearly various types of idiopathic hypertension, and perhaps to recognize those in which prophylactic venesection is most likely to be useful. Govaerts (14) has observed the phenomenon in a number of cases of hypertension, and believes that the unit osmotic pressure may be increased also. With regard to other diseases investigated, the only feature of interest is the frequency with which a moderate reduction in colloid osmotic pressure can be demonstrated. This may be due to impaired nutrition, with faulty assimilation of protein. In no case is the protein of the plasma more osmotically active than normal, since none of the points lie to the left of the normal graph.

Reduction in the volume of urine. A reduced output of urine might be attributed to diminished permeability of the glomerular capsules; but this theory cannot be entertained if we believe that these structures have become permeable to protein. Glomerular filtration may, however, be decreased by a lessened flow of blood through the kidney. Alternatively, more fluid may be reabsorbed from the tubules. Or both these causes may be operative. Oliguria is particularly characteristic of acute nephritis, and is no doubt largely due to retarded circulation in the inflamed organ. The filtrate is reduced, and more time is available for reabsorption. In these cases the blood urea is

increased. But we have less reason to suppose that the slighter reduction of the urine generally observed in chronic hydraemic nephritis is caused by such an obvious change in the circulation. Those who hold Cushny's (4) theory cannot assume the glomerular filtrate to be diminished in typical cases. For reduced filtration would result in accumulation of urea in the blood, and this does not occur in the characteristic stage of the disease. It is unnecessary to suppose that the kidneys have any inherent difficulty in excreting water, since there is every reason to believe that little water is available for excretion. Probably loss of fluid from the blood into the tissues is compensated, as far as possible, by excessive reabsorption from the renal tubules. The exact cause of this reabsorption can only be guessed. A slight general lowering of capillary blood-pressure would appear to be a possible defensive reaction to a fall in the colloid osmotic pressure of the plasma; and if this involved the tubule capillaries of the kidney, the rate of absorption might be increased. A diminution in blood-volume seems, however, a more likely cause. Recent workers have observed this in a few instances (28). More often the blood-volume was approximately normal, but in such cases the urine may have been normal in amount. At any rate, it has been shown that the blood-volume is not raised; and if the kidney is influenced at all by changes in the amount of blood in the circulation, it may well respond to a decrease undetected by the crude methods at present employed. Although capillary exudation cannot concentrate the diffusible constituents of the plasma, and although the protein is decreased by loss through the kidney, yet there is occasionally evidence of concentration of the blood as a whole. Thus, an absolute, as well as a relative, increase in the amount of fibrinogen and globulin has been found in some cases (11, 17); and a rise in the $\frac{\text{corpuscle}}{\text{plasma}}$ ratio, though often prevented by a tendency to anaemia, may occur in the earlier stages.

Retention of chloride. The total output of chloride is much reduced, and this is evidently due in large measure to escape of chloride in the oedema fluid. There is frequently, however, a rise in the percentage of chloride in the plasma. The following figures give the concentrations (expressed as NaCl) observed in a few cases:

Normal (McLean (29)).	Acute Nephritis.	Hydraemic Nephritis.
0.562-0.625	0.670	0.712
	0.719	0.645
	0.675	0.645
	0.690	0.660
	0.640	0.650

These percentages are not very much higher than those which occur in many other diseases, and they are equalled by the concentrations sometimes found in the oedema of cardiac failure. Thus in two cases of cardiac oedema the figures obtained for plasma chloride were 0.680 per cent. and 0.712 per cent. In a larger series of cases of hydraemic nephritis, higher percentages would no doubt occasionally be observed. A somewhat similar increase may occur in

azotaemic nephritis, and in that disease it seems undoubtedly due to inefficiency of the kidney. In pure hydraemic nephritis urea and other substances are concentrated very well, and renal function tests give no evidence of disease; but it is possible that, with slight impairment of the tubule cells, chloride, which is not concentrated much by the normal kidney, may be eliminated badly, while the excretion of no-threshold bodies remains unaffected. In any case, it must be remembered that the kidneys have often to excrete the usual amount of waste material in a diminished daily volume of urine, and the renal cells would have to work against an increased osmotic pressure of the tubule fluid if the output of chloride were normal. An explanation will be suggested later of chloride retention in azotaemic nephritis. It may be applicable in some degree to hydraemic nephritis also; since, although the tubule cells in this condition are less unhealthy, they are subjected to a greater strain by the higher molecular concentration of the urine. Chloride retention occurs in other diseases in which the kidney is not known to be involved; but in these there may be slight impairment of excretion, of which this is the only evidence. It occurs in diseases not associated with oedema, and can no longer be regarded as a cause of that condition.

Efficient excretion of urea. A urea content of 4 per cent. has been stated to occur in the urine of hydraemic nephritis, but the actual concentrating power of the kidney is probably somewhat lower than in health, and perhaps more chloride must be retained if a high concentration of urea is to be produced. Numerous attempts have been made to show that cells at different levels in the tubules are concerned in secreting different constituents of the urine, and, although these appear to be open to serious criticism, they may, at first sight, seem to afford an explanation of why urea should be excreted and chloride retained. But in the normal kidney chloride passes through the glomeruli at approximately its plasma concentration, and when the filtering mechanism becomes sufficiently permeable to allow the passage of protein one cannot believe that it acquires the power of holding back chloride. If the filtrate contains a normal amount of chloride, a theory of defective secretion does not readily account for a lower percentage in the urine than in the plasma—an almost invariable occurrence in hydraemic nephritis; and the view stated above with regard to reabsorption appears more likely to be correct than any conception based on a secretory hypothesis.

Causation of Albuminuria in Hydraemic Nephritis.

The cause usually assigned to this type of albuminuria is a pathological condition of the glomerular membrane. This is probably correct, but it may be of value to point out that a disorder of the plasma-producing tissues might possibly result in excretion of abnormal proteins by the kidneys. There appear to be cases of hydraemic nephritis in which an absolute increase in fibrinogen and globulin occurs; the lipoids are also increased in some cases. The theory of a primary alteration in the plasma gains some slight support from the analogy

that in pernicious anaemia the relative amounts of the plasma proteins are said to be altered (30), and retention of chloride occurs (31). But, on the other hand, such quantitative changes may be explained by supposing that the passage of fluid into the tissues occurs at a relatively more rapid rate than loss of fibrinogen and globulin in the urine; or that the loss of protein stimulates the plasma-forming tissues to increased production, which outstrips the excretion of fibrinogen and globulin, while failing to keep pace with the more rapid excretion of albumin. At any rate, an absolute increase in the globulin content of the plasma does not, as some writers infer, exclude a purely renal basis for the disease.

The decrease of protein in the plasma of hydraemic nephritis led Epstein (9) to advocate a diet rich in protein, and this treatment has given good results in some cases. It seemed possible that more rapid improvement might be produced by transfusion of blood or serum. The success of this measure would necessarily depend on better retention by the kidneys of the normal proteins injected than of those in the patient's own plasma, and on the possibility of injecting a sufficient amount to raise the existing colloid osmotic pressure to the level (about 20 cm.) at which oedema disappears. A large enough single transfusion to achieve this result in the severe cases selected could not readily be given. Two patients were transfused with about 500 c.c. of defibrinated blood (No. 2 on July 2, 1925, and No. 3 on June 30, 1925). The protein in the urine immediately increased in amount, no diuresis was observed, and when the plasma was examined several days later its colloid osmotic pressure was not found to have improved (see 2c and 3c, p. 283). Further treatment on these lines was therefore not justified. Better results, however, are to be expected from any treatment which can render the glomeruli less permeable to protein. Unfortunately, no means has yet been discovered by which this is accomplished. Calcium, although not readily absorbed from the alimentary canal, has perhaps more claim to consideration than other drugs: for there is some reason to believe that calcium lessens inflammatory exudation by reducing the permeability of capillary endothelium. This drug has been tried by various observers, though chiefly with the purpose of altering salt balance in the body fluids, or of retarding capillary exudation in all parts of the body. It seems more probable that a reduction in the loss of protein through the glomeruli explains any benefit which occurs. Very good results have been reported by several writers. Hülse (32) describes much improvement when large amounts (up to 18 gm. daily) of calcium chloride were given by the mouth, and similar success with intravenous injection of somewhat smaller quantities. Keith and Barrier (33) have obtained further evidence of the value of this treatment, by oral administration of 10-18 gm. a day. Rockwood and Barrier (34) have pointed out that calcium chloride is often successful when calcium lactate fails; and they consider that the acidosis produced by the former is mainly responsible for the diuresis observed. It is difficult to see how acidosis can result from intravenous injection of calcium chloride, although it may occur when this drug is given by the mouth. According to Keith and Barrier (*loc. cit.*) the urine is

acid while oedema is diminishing, and the alkali reserve of the patient is definitely reduced. If alkali is given, improvement ceases. These writers find that acidosis caused by ammonium chloride is also effective; and if this result is confirmed it will seem that the importance of calcium has been over-estimated. At any rate, either calcium or acidosis appears to have produced favourable effects in many cases, and it was therefore considered that a further trial would be of interest. Accordingly, each of the following methods of treatment has been practised: oral administration of calcium lactate, up to 12 grm. daily; oral administration of calcium chloride, up to 12 grm. daily; intravenous injection of calcium lactate up to 2.5 grm. daily; intravenous injection of calcium chloride up to 3 grm. daily; oral administration of ammonium chloride up to 12 grm. daily. Only three cases were available; all were severe, and had previously shown no improvement for considerable periods. No favourable change, definitely attributable to the treatment adopted, resulted from intravenous injection of either calcium salt, or from oral administration of calcium lactate or ammonium chloride. Calcium chloride given by the mouth appeared more promising. None of the methods, however, has been tried in a sufficient number of cases; and it is certainly not desired that these unsatisfactory results should discourage others from using calcium in hydraemic nephritis. This seems to be the only drug available for rational treatment, but it is possible that some essential factor in the treatment has not as yet been recognized. As regards the employment of diuretics, those of a saline type, such as urea, which are believed to act chiefly by resisting reabsorption of fluid from the renal tubules, are more likely to be successful than theobromine and caffeine, which probably act chiefly on the glomeruli. But if, as suggested, the kidneys are retaining water to compensate for loss of fluid from the blood, then diuresis may become almost impossible. And if the explanation given of chloride retention is correct, then saline diuretics, like other waste material, will tend to aggravate chloride retention. There is no evidence that moderate excess of chloride in the blood causes specific symptoms, but the possibility of disturbances in osmotic equilibrium between the cells and fluids of the body appears to justify the exclusion of salt from the diet.

Azotaemic (Chronic Interstitial) Nephritis.

This disease differs from hydraemic nephritis in that the urine is dilute, often considerably increased in amount, and generally contains a much lower percentage of albumin. These features suggest impairment of the concentrating function of the tubules rather than serious interference with filtration. Hence, if our knowledge were derived exclusively from the living kidney, hydraemic nephritis might well be regarded as mainly a disease of the glomeruli, and azotaemic nephritis of the tubule epithelium; although in the latter case slight albuminuria would often indicate some glomerular involvement. It is unsafe to place too much reliance on the histological changes ascribed to hydraemic

nephritis, for we seldom have evidence that the blood urea was normal in amount just before death, and are thus uncertain that the appearance is characteristic of a purely hydraemic stage in the disease. In azotaemic nephritis, however, the histological changes are of importance. We find that while some glomeruli and tubules are not much altered, others are partially or completely destroyed. The disease is patchy in its distribution, and generally some portions of the kidney are obviously incapable of function. We are thus compelled to deal with mixed urine from a large number of unequally impaired excretory units, and we can only consider with advantage the average condition of the kidney as a whole. In the first place, it may be inferred from the presence of albumin in the urine that the permeability of the filtering membrane is not diminished; and heightened blood-pressure may cause even more rapid filtration than usual through some of the glomeruli. There is no evidence as to whether the total filtrate is normal in amount. Two-thirds, or more, of the normal kidney tissue may be removed from animals without causing serious interference with excretion. In fact, the removal of kidney substance causes diuresis (35), and we may suppose that filtration through the remaining glomeruli occurs more rapidly than usual. It is unlikely that all the glomeruli of the normal kidney are continually in action, for the great variations observed in renal blood-flow (36), and in the number of glomeruli visible when the living kidney of the frog is examined microscopically (37), suggest that there is a considerable reserve available for periods of excessive activity. Hence it is quite uncertain that the amount of filtrate is reduced in azotaemic nephritis; and even if this were assumed to be the case, certain characteristic changes in the urine would have to be accounted for in some other way.

Secondly, the limit to concentration by the tubule cells of the normal kidney is probably imposed by the osmotic resistance of the fluid in the tubules (4), although in health this limit is largely theoretical and can only be reached in rare conditions of very slow excretion, when sufficient time is allowed for an equilibrium to be established. By equilibrium is meant a condition in which the total molecular concentration of the fluid has become so high that the tubule cells are unable to produce any further increase. In azotaemic nephritis the less altered glomeruli are doubtless in a state of hyperactivity, while those through which the blood-flow is restricted by fibrosis are not so active as usual. The urine is derived chiefly from the less unhealthy portions of the kidney, where the passage of fluid down the tubules is rapid, and the conditions unfavourable for concentration. But in spite of this it seems justifiable to believe that in azotaemic nephritis a state of equilibrium can more readily be attained than in the normal kidney, because the glomerular filtrate contains urea in already abnormally high concentration, and also because the diseased tubule cells are unable to overcome so great an osmotic pressure as in health. For these reasons, the limit is reached without so much secretion of solids or absorption of water.

With the purpose of examining from this aspect the problems of excretory

TABLE V.

Case.	Specimen.	Period (hours).	Volume (c.c.).	Δ ° C.	NaCl (gm. %).	Urea (gm. %).
1.	Plasma	—	—	0.655	0.630	0.261
	Night urine	10½	691	0.618	0.337	0.690
	Day 1	2	210	0.600	0.325	0.705
	" 2	2	60	0.640	0.320	0.756
	" 3	2	128	0.615	0.290	0.744
	" 4	2	154	0.625	0.275	0.642
	" 5	2	114	0.610	0.290	0.651
2.	Plasma	(Taken during Day 3)	—	0.635	0.610	0.348
	Night urine	10	640	0.580	0.277	0.744
	Day 1	1½	420	0.600	0.295	0.744
	" 2	2	280	0.560	0.269	0.720
	" 3	2	196	0.562	0.295	0.720
	" 4	2	173	0.625	0.285	0.768
	" 5	2	196	0.575	0.272	0.792
3.	Plasma	(Taken during Day 3)	—	0.616	0.560	0.339
	Night urine	10	402	0.706	0.080	1.194
	Day 1	1½	37	0.695	0.070	1.248
	" 2	2	81	0.664	0.090	1.254
	" 3	2	107	0.642	0.132	1.158
	" 4	2	105	0.724	0.185	1.242
	" 5	2½	95	0.660	0.125	1.158
4.	Plasma	(Taken during Day 3)	—	0.522	0.510	0.075
	Night urine	12	538	0.625	0.305	0.678
	Day 1	2	28	0.650	0.235	0.738
	" 2	2	202	0.450	0.315	0.354
	" 3	2	97	0.670	0.252	0.708
	" 4	2	128	0.545	0.290	0.540
	" 5	2	72	0.665	0.270	0.786
5a.	Plasma	(Taken during Day 4)	—	0.562	0.635	0.109
	Night urine	9	545	0.662	0.205	1.050
	Day 1	2	96	0.660	0.153	1.140
	" 2	2	110	0.738	0.280	1.113
	" 3	2	76	0.807	0.225	1.374
	" 4	2	100	0.648	0.212	1.050
	" 5	2	230	0.352	0.095	0.582
5b.	Plasma	(Taken during Day 4)	—	0.632	0.750	0.124
	Night urine	9	506	0.738	0.252	1.104
	Day 1	2	82	0.740	0.205	1.152
	" 2	2	115	0.750	0.260	1.164
	" 3*	2	110	0.737	0.275	1.014
	" 4	2	110	0.785	0.390	0.978
	" 5	2	137	0.745	0.432	0.882
5c.	Plasma	(Taken during Day 3)	—	0.617	0.720	0.168
	Night urine	10	532	0.662	0.240	0.900
	Day 1	2	57	0.750	0.233	1.050
	" 2†	2	155	0.740	0.275	0.984
	" 3	2	115	0.770	0.335	0.936
	" 4	2	127	0.789	0.420	0.930
	" 5	2	160	0.725	0.437	0.816
6a.	Plasma	(Taken during Day 2)	—	0.610	0.695	0.135
	Night urine	10	697	0.832	0.237	1.392
	Day 1	2	102	0.835	0.217	1.362
	" 2	2	86	0.845	0.125	1.482
	" 3	2	71	0.893	0.097	1.584
	" 4	2	93	0.891	0.132	1.500
	" 5	2	117	0.910	0.115	1.572
6b.	Plasma	(Taken during Day 1)	—	0.627	0.670	0.291
	Night urine	14½	233	0.717	0.021	1.470
	Day 1	7	167	0.727	0.018	1.483

* 3ii sod. chlorid. taken during the first hour of this period.

† 3iii sod. chlorid. taken during the second hour of this period.

failure, some observations have been made on the reduced concentrating power of the kidney in azotaemic nephritis. The depression of freezing-point and the concentrations of urea and chloride were determined in the plasma and urine of a number of patients. The urine was collected at night, and in two-hourly samples during most of the following day, so that the total output for approximately twenty hours was obtained; and a specimen of blood was taken from a vein during the collection of one of the samples of urine. Heparin was again employed as an anticoagulant. The results of these experiments are given in Table V.

These experiments cover periods of 19-22 hours, and should show any variations which were likely to occur in the urine of the patients.

In Cases 1 and 2 the kidneys are very inefficient, and the molecular concentration of the plasma, as indicated by the depression of its freezing-point, is much greater than normal; this is largely due to retention of urea. The depression of freezing-point for normal plasma is about 0.56°C . The kidneys fail, throughout the experiment, to raise the total molecular concentration of the urine above that of the plasma, and the concentration of the urine remains very constant. The freezing-point of the plasma is, in fact, rather lower than that of any of the samples of urine, but this may be due to loss of CO_2 from the urine, or to some other experimental error. Urea is concentrated to some extent, while the concentration of chloride is reduced; so that the kidneys still exercise some power of choice in the matter of excretion, although they are unable to concentrate the urine as a whole.

Case 3 presents similar features, but the kidneys retain a negligible concentrating power, which was altogether absent in the first two cases. The chloride content of the plasma is near the threshold value (29), and the amount in the urine is thus unusually small, even for this type of case. This condition may favour excretion of urea.

In Case 4 the freezing-point depression of the plasma is not so great as in health. This appears to be due chiefly to an abnormally low chloride content, while the plasma urea is not increased nearly so much as in the previous cases. The low percentage of chloride may have been the result of prolonged diuresis, which may also have assisted elimination of urea; but of this there is no direct evidence. Although the molecular concentration of the urine is low, the kidneys can still excrete urine either more concentrated or more dilute than the plasma. In spite of a plasma chloride content below the suggested threshold value the urine contains an amount similar to that of the first two patients.

Case 5 is a typical example of azotaemic nephritis, but illustrates no points of importance to which reference has not already been made. Neither in this nor in the previous cases is the chloride content of the plasma abnormally high, and it was considered advisable to exclude the possibility that the low concentration of chloride in the urine might be due merely to a diminished intake in the diet, and not to renal inefficiency. On two occasions, therefore, salt was given to this patient (5b 8 gm., and 5c 12 gm.), with the smallest convenient amount of

extra fluid. The plasma chloride on each occasion rose to well above 0.7 per cent. (expressed as NaCl), but the urine concentration, although somewhat increased, did not approach that in the plasma; and although the output of urine was somewhat greater, the low chloride content could not be ascribed to diuresis. The kidneys, therefore, fail to excrete chloride satisfactorily, and the normal plasma chloride in patients under hospital treatment must be largely due to restricted diet; but another reason for the absence of chloride accumulation will be given later, when the mechanism of excretion is discussed.

Two observations were made in Case 6. In the first of these the freezing-point depression of the plasma is considerably increased, and this patient shows accumulation of chloride as well as urea. The kidneys are able to concentrate the urine more than was possible in the previous cases; and if their condition were to be judged by urea excretion alone, they might seem relatively efficient. But in spite of the high chloride content of the plasma, the concentration of this substance in the urine remains as low as in most of the other cases. The second observation was made about a month later, just before death, and cardiac oedema had occurred. The patient was then very anaemic. An insufficient amount of plasma was obtained, and the freezing-point depression given is probably only approximate. Samples of urine could not be collected when desired. The slight lowering of plasma chloride is probably a transient phenomenon, associated with the onset of oedema, which would presumably necessitate the distribution of available chloride through a larger volume of fluid. The kidneys are apparently rather less capable of concentration than before, for although chloride is almost absent from the urine they have not taken advantage of this facility for concentrating urea more effectively. It is probable that oedema, rather than renal inadequacy, is responsible for the more complete retention of chloride; and death seems to have been due to anaemia and cardiac failure, rather than to a complete break-down of the excretory function.

In discussing these results two features demand special attention. The first is an apparent reduction in the power of the kidney to produce a change in concentration against osmotic resistance. This is shown, in two cases of extreme urea retention, by the close resemblance between the depression of freezing-point of the urine and that of the plasma; in the remaining cases, by a smaller difference than is usual in health. The second feature, which is common to all, is the consistent manner in which the chloride content of the urine is reduced below that of the plasma. The same characteristic has been observed by O'Hare (38), in cases with increased blood urea; and, although routine chloride determinations for clinical use are seldom made in the absence of oedema, an examination of such hospital records as could be collected locally tended to confirm the existence of this phenomenon in advanced azotaemic nephritis.

The evidence we possess with regard to glomerular function is in favour of the view that this is merely a process of filtration. In disease the nature of the process is unchanged, but the permeability of the membrane may increase, and proteins may escape in the filtrate. In no case is there evidence of lessened

permeability to dissolved substances; and those who assume that this condition can arise must accept the necessary implication that work is done by the cells of the membrane in separating water from the substances which are retained. This is an unlikely theory, and it is fairly safe to suppose that the only qualitative change in filtration is the escape of protein. We are now able to make two deductions from the results shown in Table V. The first is that in very severe azotaemic nephritis the tubule cells are unable to alter appreciably the total molecular concentration of the glomerular filtrate. The second is that, however advanced the disease, the composition of the filtrate is always changed by these cells, even when the total molecular concentration is unaltered. Since filtration alone produces no significant change in the relative proportions of the substances filtered, the occurrence of less chloride in the urine than in the plasma is probably due to reabsorption of chloride by the tubule cells. It will be assumed that secretion is not one of the functions of the kidney, but that the concentration of urine is entirely due to absorption of water.

Reasons have already been given for believing that the limit which osmotic pressure imposes on concentration by the renal epithelium is more easily reached in azotaemic nephritis than in the normal kidney. If the tendency to reabsorb water remains unabated, the resistance of the tubule cells to substances dissolved in this water may break down. There is evidence that in the kidney of the rabbit absorption of urea takes place when the molecular concentration of the tubule fluid becomes unusually high (39). The suggestion was made in a previous paper that urea may be absorbed by the tubule epithelium of the diseased human kidney (40), and this possibility has also been pointed out recently by Dunn and Jones (41). The normal tubule cells differ from those of other tissues in the resistance which they offer to the passage of urea; in azotaemic nephritis this difference is not so great as in health. But the resulting failure of urea elimination is probably avoided to some extent by excessive reabsorption of chloride. There is no reason to assume that in disease the renal cells fail to distinguish between the constituents of the glomerular filtrate, though all of these are resisted less strongly. Thus, the normal kidney excretes creatinine more efficiently than urea, and the latter more efficiently than uric acid; and in nephritis creatinine retention occurs later than retention of urea, while uric acid seems to be retained at an earlier stage (42). In health, most of the chloride which filters through the glomeruli is reabsorbed, while most of the urea is rejected; and in azotaemic nephritis the kidney continues to excrete urea more effectively than chloride (38). It does not follow that chloride necessarily accumulates in the blood, for in the case of chloride a much higher proportion of the total amount in the filtrate can be reabsorbed without causing accumulation than in the case of urea and other substances; because the concentration of chloride in the filtrate is so much greater that excretion of a very small percentage of the filtered salt is sufficient to balance the daily intake. The observation of Underhill, Wells, and Goldschmidt (43), that in rabbits with tartrate nephritis injected chloride is excreted more rapidly than injected urea,

cannot be accepted as evidence of greater efficiency in chloride excretion, since the plasma content of this substance was probably higher. The kidney appears to have concentrated urea, but not chloride (except, perhaps, in one instance); and thus the more rapid output of chloride—in spite of greater reabsorption—must be explained by the presence of a larger amount in the glomerular filtrate.

It should be observed that while the absorption of urea in azotaemic nephritis may be looked upon as a mere passive diffusion of part of the filtered urea through the diseased tubule cells—a lowered resistance of the cells to urea—the absorption of chloride must certainly be regarded as active. For chloride is evidently reabsorbed in a more concentrated solution than that which it forms in the glomerular filtrate; otherwise the urine could not contain less than the plasma. No such effect could result from diffusion alone. This active reabsorption of chloride occurs even when the plasma concentration is already too high; and chloride thus differs from other components of the glomerular filtrate, which are absorbed in a solution less concentrated than that in which they are filtered, and appear to undergo a sort of imperfectly resisted diffusion rather than true absorption. The contrast has not hitherto been emphasized, nor has the difficulty which it raises been appreciated.

It seems clear that the active reabsorption of chloride in disease is an inevitable result of the natural preference for chloride possessed by the tubule cells. We have no reason to suppose that osmotic resistance ever completely inhibits absorption of fluid. It is only necessary to assume that as this force increases the fluid absorbed becomes more similar in molecular concentration to the fluid remaining in the tubules. In the normal kidney a condition of this kind can hardly occur, owing to the high resistance of the tubule cells to urea, and the retardation of absorption by increasing osmotic pressure. In advanced azotaemic nephritis, however, when the total molecular concentration of the urine is almost the same as that of the plasma, we can scarcely doubt that the osmotic limit has been reached; it may perhaps be reached in earlier cases also, when failing concentration is observed without much diuresis. And so, in the process of concentration, chloride and urea both pass into the tubule cells; the return of urea, which tends to diffuse through as the osmotic resistance to water absorption increases, being limited to some extent by active reabsorption of chloride, by which the rise in osmotic resistance to water absorption is rendered less rapid. There is no evidence of failure of selective power; concentration of urea is still possible, but is continued at the cost of a reduction in chloride excretion. A good analogy is provided by the normal gall-bladder, in which liver bile is concentrated by removal of water. Inorganic salts are absorbed in greater proportion than water, and, although the content of bile-salts may be increased to 10 per cent. or more, the osmotic pressure of the bile does not rise (44). The molecular concentration cannot be increased because the cells of the gall-bladder have no power to absorb water against an osmotic resistance.

As the disease advances the permeability of the tubule cells to no-threshold bodies undergoes a progressive increase, and accumulation of creatinine occurs;

but even in the latest stages the capacity for active reabsorption of chloride appears to be preserved.

Since the power of the kidney to concentrate waste-products is reduced, the patient's life must depend on diuresis. In the absence of oedema, it seems rational to give a considerable amount of fluid. From a theoretical standpoint caffeine or theobromine should be of value, since these drugs appear to act chiefly by increasing glomerular filtration. But it may be doubted whether they could alter an output of urine already considerable, and in practice they have been said to prove injurious (45). The question requires further clinical investigation. Saline diuretics are inadmissible, since they have no specific effect, but act in the tubules as no-threshold bodies, and merely increase the amount of waste material to be eliminated.

Summary.

The chief symptoms of *hydraemic nephritis* seem to result more or less directly from lowering of the colloid osmotic pressure of the plasma, probably itself due to loss of protein through damaged glomeruli. The colloid osmotic pressure can no longer offer sufficient resistance to the blood-pressure in the capillaries, and excess of fluid is forced through the capillary endothelium into the tissues. Oedema occurs, and tends to concentrate the blood. This concentration may be shown by an absolute increase in the globulin content of the plasma, provided the loss of globulin in the urine is not too rapid; and also, in the absence of anaemia, by an increased $\frac{\text{corpuscle}}{\text{plasma}}$ ratio. The resulting change in the circulation is probably slight in most cases, but appears sufficient, as a rule, to cause the renal epithelium to reabsorb more water than usual. Excretion of urea may be rendered more efficient by the active reabsorption of chloride, and thus the tubule cells, though slightly impaired, are enabled to give a normal response to tests of renal function, and to eliminate waste products satisfactorily.

In *azotaemic nephritis* many of the glomeruli retain their permeability, but it is impossible to determine whether a sufficient number remain in action to produce the normal amount of filtrate. The tubule function of concentration is seriously impaired. In severe cases the total molecular concentration of the urine may never be greater than that of the plasma, and this is interpreted as a complete failure of the tubule cells to overcome osmotic resistance. But these cells always succeed in altering the composition of the glomerular filtrate, and, while urea is always concentrated to some extent, the urine of advanced azotaemic nephritis never contains as much chloride as the plasma. The explanation suggested is based on the idea of an equilibrium at an osmotic resistance which the tubule cells cannot overcome, and at which normal reabsorption can no longer proceed. When this equilibrium is reached, or even before it is reached, undesired substances begin to diffuse back through

the tubule cells. Some of these are resisted more strongly than others (i. e. selective power is retained), but the fluid absorbed is no longer 'optimal fluid'. Chloride, the substance least distasteful to the cells, is actively taken up from the glomerular filtrate, and reabsorption of water can thus be continued with less backward diffusion of the more harmful waste products. Evidence is given in support of this view.

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THE INHERITANCE OF EPILEPSY¹

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Introduction.

ANY ONE wishing to ascertain from the literature the part played by heredity in the aetiology of epilepsy would find it difficult to reach a conclusion from the confused and conflicting material available. Myerson (7), writing in 1925 on the inheritance of mental diseases, is able to conclude even that 'the hereditary factor in epilepsy has not been proven to exist'. Many of the investigations still quoted were conducted from thirty to fifty years ago, when our present knowledge of the specificity of inherited characters was lacking. Investigators therefore sought in general terms for evidence of 'neuropathic inheritance', which ranged from undefined insanity through epilepsy to 'hemiplegia', 'migraine', and even 'strabismus'. Frequently the proportion of 'neuropathic' ancestors who were actually epileptic is not stated. The precise nature of 'neuropathic' manifestations among relatives or ancestors is usually incapable of being established, and, since controls are almost invariably lacking, the aetiological connexion between these diseases and epilepsy remains what it was to begin with—an assumption.

This paper is both a review of opinions which have from time to time been advanced on the subject of the inheritance of epilepsy and an attempt, by means of a fresh investigation, to throw light on some of its aspects. It embodies the results of an inquiry into the family history of a series of over 200 epileptics whom I have personally seen in the Out-patient Departments of the London Hospital and the Hospital for Epilepsy and Paralysis, Maida Vale. By epilepsy is understood that clinical condition, commonly called idiopathic epilepsy, which is characterized by recurrent attacks of loss of consciousness, with or without generalized convulsions, occurring in persons who show no physical signs of organic disease in the nervous system due to congenital abnormality, syphilis or other infection, or trauma.

The Incidence of Epilepsy among the Relatives of Epileptics.

The incidence of epilepsy among the relatives of epileptics has been variously estimated by different workers. Clarke (2), in a small series of criminal epileptics,

¹ Received Feb. 8, 1926.

found a family history of epilepsy in 46 per cent. of the males and in 70 per cent. of the females. His patients, who were all imprisoned criminals, cannot be considered as representative of the general population. Turner (13) found 'ancestral epilepsy' in 37 per cent. of his series of 890 epileptics. Echeverria (4) reports that 42 epileptics in a series of 136 had epileptic relatives, i.e. 30 per cent. Gowers (5) uses the term 'inherited epilepsy' to describe cases with a family history of either epilepsy or insanity. This has led to confusion, since writers quoting Gowers have usually interpreted the phrase as indicating a family history of epilepsy itself, whereas this was not present in about one-third of the cases of 'inherited epilepsy' as Gowers understood the term. Actually in his large series of 2,400 epileptics, 655 gave a family history of epilepsy, or about 27.3 per cent. Clarke (2) quotes Bennett as having found a family history of the disease in 26 per cent. of 100 epileptics. Among the lower figures obtained are those of Binswanger (1), who found it in 11 per cent. of a series of 121 cases; Déjérine and Moreau, quoted by Binswanger (1) as having found it in 21 per cent. and 16 per cent. respectively; Davenport and Weeks (3), who found it in 19 per cent.; and Reynolds (10), who found it in 12 per cent.

In my own series the family history has been investigated in 200 epileptics. A mere general inquiry as to the presence of the disease in the family was considered valueless. Gowers relates that the mother of an epileptic child, after denying that any relatives were epileptic, shortly returned with the child's two epileptic brothers. She regarded brothers as too closely connected to be considered 'relatives'. In every case, therefore, the patient or a near relative has been specifically asked about all near relatives, mentioning the relationship by name. Information has in this way been obtained in every case concerning grandparents, parents, uncles, aunts, first cousins, and siblings, and in some cases also concerning the parents' uncles, aunts, and cousins. An objection raised by Myerson (7) may be dealt with here. He considers that epilepsy in relatives other than those in the direct ancestral line 'can only have a very indirect bearing, since the germ-plasm, let us say of a cousin, is in only a fraction similar'. This implies a return to the ideas of Weismann, who held that the germ-plasm is quantitatively parcelled out in inheritance, so that a grandchild, for example, cannot receive more than one quarter of the hereditary material of any one of his grandparents, which is thus diluted by the hereditary material derived from the other three. All modern experimental work in genetics goes to show that unit hereditary characters are usually handed on as units, so that in the case of many characters all the grandchildren of one grandparent may exhibit the character in question as fully as the grandparent. This is the justification for inquiring into the occurrence of epilepsy in, for example, cousins of epileptic patients.

Of my 200 patients, 56 had a family history of epilepsy, or 28 per cent. It will be noted that this figure is in substantial agreement with those found by Turner (37 per cent.), Echeverria (30 per cent.), Gowers (27 per cent.), and Bennett (26 per cent.). There can be little doubt, as Gowers observes, that,

owing to lack of information among hospital patients concerning their relatives, and sometimes to wilful suppression of the facts, these figures are too low. As a control, similar inquiries as to the presence of epilepsy in the family history have been made of 100 patients attending for nervous diseases other than epilepsy in the Out-patient Department of the Maida Vale Hospital. Of these, ten gave a family history of epilepsy, or 10 per cent. This figure is very probably higher than that which would be obtained in the general population, since four of the ten who gave a family history of epilepsy had had epileptic relatives treated at the hospital, and would probably not otherwise have come into the count.

The Distribution of Cases in Affected Families.

The distribution of cases of epilepsy in the 200 families is of considerable interest:

TABLE I.

Number of affected persons per family	1	2	3	4	5	6
Number of families	144	43	5	5	2	1

TABLE II.

Number of generations containing affected persons	1	2	3	3 skipping 1
Number of families	158	30	5	7

Tables I and II show the relative frequency of families containing from one to six affected members, and of the occurrence of the disease in from one to three generations.

TABLE III.

Relationship.	Number of times recorded.
Parent and child	32
Uncle or aunt and nephew or niece	31
Siblings	30
Grandparent and grandchild	11
First cousins	8
Remoter relatives	11
Total	123

In Table III are shown the relationships subsisting between the affected persons in the fifty-six families in which two or more persons were affected, and the frequency of their occurrence. Owing to the small numbers no reliable information would be obtained from distributing them according to sex.

Myerson states that he rarely sees brothers and sisters who are epileptic, and that in the Massachusetts State Hospital for Epileptics, containing 1,500 patients, there are only four such families, consisting of eleven people. It is worthy of note, therefore, that the writer's series of 200 epileptics yielded information concerning twenty-four families with two or more affected siblings,

there being two affected in twenty-one families and three affected in three families. In two families a half-brother and half-sister were affected, the father in one instance and the mother in the other having begotten an epileptic child by each of two conjugal partners.

Heredity in Relation to Sex, and Age of Onset.

Gowers (5) notes that inheritance does not affect the two sexes equally. In the figures which he gives bearing on this point he does not differentiate between epilepsy and insanity in the family history, but, taking the two conditions together, demonstrates that 'where there is an inherited taint the females of a family are more likely to suffer than the males'. This is confirmed by the present investigation, for while 23.8 per cent. of epileptic males gave a family history of epilepsy, this was present in the case of 31.2 per cent. of epileptic females.

Clarke (2), Reynolds (10), and others state that epilepsy is more often inherited through the mother than through the father. Gowers also, using the combined figures for epilepsy and insanity, states that the inheritance is more often maternal than paternal. But the difference is negligible in the case of epilepsy alone, at any rate in the direct line, since in Gowers' series of 762 cases of inherited epilepsy the father was epileptic in 87 and the mother in 91 cases. The opposite conclusion of Clarke and Reynolds must be attributed to the comparatively small number of their cases.

Of considerable interest is the influence of an inherited predisposition on the age of onset of convulsions. This is ascertainable from Table IV, in which those patients in whose cases the age of onset of the disease was known are distributed according to the age of onset and the presence or absence of a family history of the disease. Age of onset here indicates the age at which the patient began to suffer from recurrent attacks, the relation between infantile convulsions and epilepsy being considered in a separate section.

TABLE IV.

Age of Onset.	Percentage of Total in Group without Family History of Epilepsy.			Percentage of Total in Group with Family History of Epilepsy.		
	Males.	Females.	Both Sexes.	Males.	Females.	Both Sexes.
0-9	20.7	16.4	37.1	22.6	27.4	50.0
10-19	18.6	27.1	45.7	11.3	21.0	32.3
20 or older	7.9	9.3	17.2	4.8	12.9	17.7

It will be seen that 50 per cent. of those with a family history of the disease begin to have fits during the first decade of life, as compared with 37 per cent. of those without such a family history, whereas the onset occurred in the second decade in a greater proportion of those in the latter class. This fact suggests that those who have an inherited predisposition to epilepsy tend to

become epileptic at an earlier age than those who are not thus predisposed. Gowers denies this, but about one-third of the patients in his group of cases of 'inherited epilepsy' are included on account of a family history of insanity alone. Since, as will be shown later, there is little evidence that insanity is related to epilepsy, this amounts to a large dilution of the 'inherited group' with cases that should be in the group without inheritance, and would tend to make the two groups similar in respect of age of onset.

Inherited Epilepsy and Infantile Convulsions.

Patrick and Levy (9) have compared the incidence of early convulsions in a group of 500 epileptics and in a group of 752 unselected infants and children. They found that early convulsions were five times as common in epileptics as in normal children, occurring in 20 per cent. of the former and 4 per cent. of the latter. They consider that, owing to defective histories obtained in the case of epileptics in whom fits began in the third decade, the figure of 20 per cent. is too low, and that it is probable that early convulsions occur in about 40 per cent. of epileptics. These authors found that the early convulsions differed in epileptics and non-epileptics in respect of number, age of onset, type, and assigned cause. In the case of the normals early convulsions are usually single, occur mostly between the ages of 6 and 17 months, are brief and less commonly followed by confusion or prolonged stupor, and are usually attributed to teething. In the epileptics the convulsions are more often multiple: 63 per cent. occur below the age of 6 months or after the age of 17 months, while the commonest cause is trauma, especially birth trauma, though to many no cause can be assigned. In both groups males are more often affected than females, in the proportion of 3 to 2. Patrick and Levy note that among their non-epileptic children who had had early convulsions a family history both of early convulsions and of epilepsy was much commoner than among those who had not.

In the writer's series definite information as to the occurrence of early convulsions was obtainable in the case of 176 epileptics. Of these, 50, or 28 per cent., either had had early convulsions or had been epileptic since infancy. These 176 patients were arranged in two groups according to the presence or absence of epilepsy among the relatives. In the 'hereditary group' there were 51 cases, of whom 13 had been epileptic from infancy and 8 had had early convulsions, a total of 41 per cent. In the group without a family history of the disease there were 125 cases, of whom 16 had been epileptic from infancy and 13 had had early convulsions, or 23 per cent. Thus, early convulsions were nearly twice as common in epileptics with a family history of the disease as in those without. It is evident, therefore, that both epileptics and non-epileptics who have a family history of epilepsy are much more likely to have infantile convulsions than those who have not.

In this series, as in Patrick and Levy's, early convulsions were rather more

common in males than in females, since they occurred in 28 males and 22 females.

The Incidence of Epilepsy among the Offspring of Epileptics.

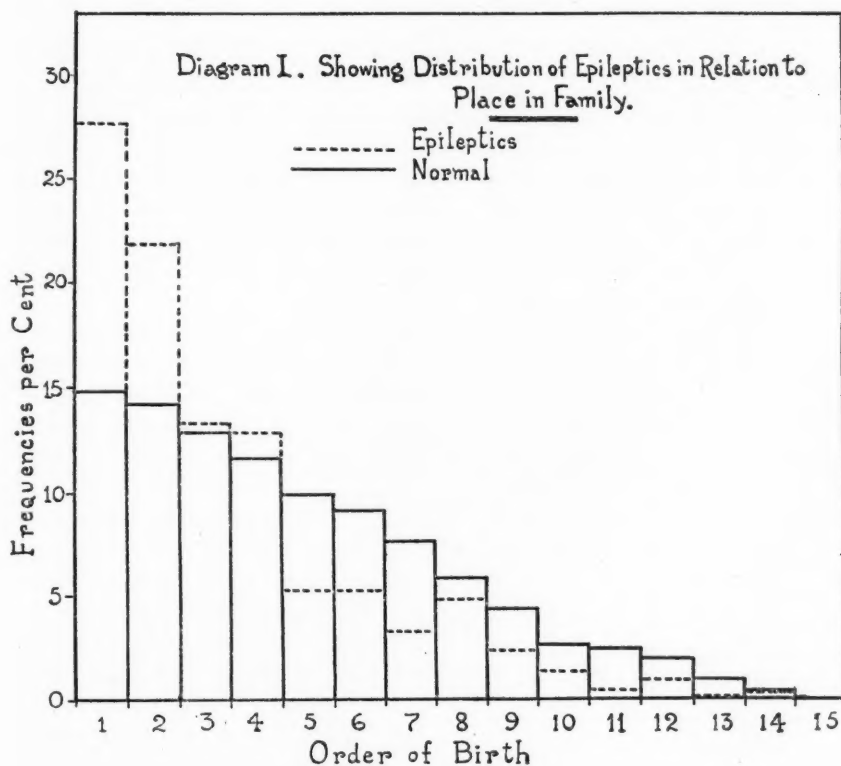
Many workers have noted the comparative infrequency of direct inheritance in epilepsy. In this series of 200 epileptics the number born of an epileptic parent was 15 or 7.5 per cent. Table III shows all the relationships subsisting between affected persons in the 56 families in the series which contained more than one affected member. It will be seen that the relationship of parent and child occurs 32 times out of 127, i.e. it forms 25 per cent. of the total. The same relationship may be investigated in another way. What proportion of the children of epileptics become epileptic? Less information is available on this point, and the results obtained by two authorities, Echeverria (4) and Thom (12), are widely divergent. Echeverria found that 136 married epileptics had a total of 533 children, of whom 195 died in infancy of convulsions and 78 became epileptic, while Thom found that a similar series of 138 epileptics begot 553 children, of whom 6 died in infancy of convulsions and 4 became epileptic. It seems useless to speculate as to the cause of this divergence. In the writer's own series there is a much smaller number of married epileptics, viz. 24, with a total of 56 children, of whom 3 are epileptics, three of the epileptic parents having given birth to one epileptic child each. Approximately 1 in 20 of the children of epileptic parents therefore appears to become epileptic, but in view of the small numbers on which this result is based, little weight can be attached to it.

The number of instances in which transmission of the disease from epileptic parent to child occurs may at first sight appear small. But it must be remembered, first, that only 28 per cent. of one generation of epileptics are known to be derived from families containing closely related epileptic members, and, secondly, that the hereditary cases in the second generation appear not only among the children of epileptics, but also among the children of their unaffected brothers and sisters and other relatives.

The Incidence of Epilepsy in Relation to Place in Family.

It appeared worth while to investigate whether the place occupied by the patient in his family was of any aetiological importance. To ascertain this it is necessary simply to compare the relative frequency with which the successive positions in the family occur in a series of epileptics with the relative frequency of their occurrence in the non-epileptics in the section of the population from which the patients are drawn. The relative frequency of first-born, second-born, &c., children in the general population clearly depends upon the relative numbers of one-child, two-child, &c., families. Information on this point was obtained from non-epileptic patients attending the Out-patient Department of the London

and Maida Vale Hospitals. This group, which may be called normal, yielded information concerning 876 persons who were distributed according to their place in the family from first- to fifteenth-born. The number for each place in the family was expressed as a percentage of the total. It may be mentioned that in the section of the population attending hospital there is a relative preponderance of large families, and hence of later-born persons, compared with the figures for the general population calculated from data obtained in the report on the 1911 census.



210 epileptics were then distributed according to their place in the family and the numbers for each place expressed as a percentage of the total. The two series appear in Table V and are expressed graphically in Diagram 1.

TABLE V.

Place in Family.	1	2	3	4	5	6	7	8	9	10	10+
Percentage of normals (hospital population)	14.8	14.1	12.9	11.6	9.9	9.1	7.6	5.8	4.4	3.6	6.2
Percentage of epi- leptics	27.6	21.9	13.3	12.9	5.2	5.2	3.3	4.8	2.4	1.4	1.9

The preponderance of first- and second-born children among the epileptics is striking. It will be seen that these two groups constitute almost 50 per cent. of the total. The proportion of first-born among the epileptics is almost double that in the normal section of the population, that of the second-born half as large again as the corresponding normal group. The later-born, fifth-born and downwards, occur correspondingly less frequently among epileptics. The significance of this difference will be discussed in a later section.

The Incidence of Insanity among the Relatives of Epileptics.

Owing to the practice of including insanity in some more general term, such as 'neuropathic taint', there is little information to be obtained from previous investigations as to the incidence of insanity among the relatives of epileptics. Gowers (5) found a family history of insanity among the relatives of 13.6 per cent. of his series of 2,400 epileptics. Binswanger (1) quotes Moreau as having found it in 11 per cent. of a series of 364 patients, and Déjérine as having found it in 16.8 per cent. of a series of 244. Turner (13) found ancestral insanity in 4.8 per cent. of his series of 890 epileptics. None of these authors state their criterion of insanity.

In the writer's series only those relatives have been counted as insane who were admitted to asylums for conditions other than epilepsy or mental defect. Three, for whose insanity there was no evidence other than that they committed suicide, have been omitted. Of 200 families, containing one or more epileptic members, there was a family history of mental disease in only 16, there being in these 16 families 20 cases of insanity. It is doubtful whether an incidence of 8 per cent. is much above that of a family history of insanity in the population in general. According to the Annual Report of the Board of Control for 1924 there were 131,551 notified cases of mental disease in England and Wales on January 1, 1925, the population at that time being 37,885,242. The proportion of notified insane in the general population was therefore approximately 3.5 per 1,000. If we assume that we obtain in the case of each epileptic patient information concerning 20 relatives the investigation of 100 epileptics would cover 2,000 members of the general population and would be expected to yield 7 insane persons, whereas the number actually obtained was 10. In view of the conjectural character of the former figure, little significance can be attached to this difference. There was no evidence that families containing more than one epileptic contained proportionately more insane persons.

The Evidence for Predisposition as an Aetiological Factor in Epilepsy.

Two conflicting views concerning the aetiology of epilepsy are expressed in the following statement by Oppenheim and in Myerson's comment upon it. 'A number of conditions', says Oppenheim (8), 'are capable of producing it, but

apparently they make their influence felt chiefly when the morbid predisposition is already present'. 'Why invoke predisposition', replies Myerson, 'when a condition can produce epilepsy by itself? . . . Any one may get epilepsy if a lesion be placed properly.' Can a study of the inheritance of epilepsy throw any light upon its aetiology or help to decide between these two hypotheses? The establishment of the fact that about 30 per cent. of epileptics have a family history of the disease seems to necessitate an acceptance of the theory of predisposition for this group at least. It is difficult to believe that what is inherited is the appropriate lesion, which, moreover, gives no clinical indication of its presence. Myerson evades this difficulty only by denying the inheritance of epilepsy altogether.

There is another group of cases which lends support to the view expressed by Oppenheim. In collecting this series of cases, nine patients have been met with in whom there was present not only a lesion such as Myerson considers adequate to account for their convulsions, but also a family history of epilepsy. In five cases the lesion was injury to the head, two had acquired syphilis, and two were cases of infantile hemiplegia. It is difficult to resist the conclusion that in these patients the acquired lesion precipitated the convulsions by activating an inherited predisposition.

The high incidence of early convulsions in epileptics suggests that in patients suffering from this disease there has often been a predisposition to convulsions present from birth, and this is confirmed by the observation that early convulsions are almost twice as common among epileptics with a family history of the disease as in those with none. In the former class, also, the attacks begin during the first decade of life in a larger proportion of cases than in the latter. All these considerations suggest that predisposition plays at least as great a part in the aetiology of epilepsy as does the acquisition of a cerebral lesion.

It is not proposed in this paper to consider at length the evidence for the presence of an additional precipitating factor, but one fact bearing on this aspect of the problem has emerged in the course of the investigation. It is well known that a history of a head injury preceding the onset of the attack is frequently given by epileptic patients or their relatives. Although such a history must not be accepted uncritically, the association of head injury and epilepsy has been so frequently described that there can be little doubt that in a number of cases the injury is indeed the precipitating factor. The high proportion of epileptics who are first-born children is capable of several possible explanations. It may be that the maternal organism is less prepared to meet the demands made upon it by a first pregnancy than by later ones, and that for this reason the first child is more likely to be abnormal; or even that the earlier children are more likely to suffer from unsuitable diet as a result of maternal inexperience. These explanations, however, are hypotheses. It seems more likely that the cause is the greater liability of first-born children to head injury during birth, which is a well-established fact. Some light is thrown on this

point by a comparison of the percentages of first-born children in this series of epileptics and in a series of newly-born children dead as a result of head injury. It will be remembered that 27.6 per cent. of 211 epileptics were first-born. Eardley Holland (6) has published particulars of 81 cases of foetal death from tears of tentorium cerebelli. Of these, 28, or 34.5 per cent., were first-born children. Both series were drawn from the hospital population, in which the first-born constitute about 15 per cent. It is evident that the increased liability of the first-born to become epileptic is roughly commensurate with their increased liability to suffer gross intracranial birth injury.

It seems reasonable to suppose that they are also more liable than later-born children to receive during birth less severe cerebral injuries from which recovery may be apparently complete, but which may in later life become the precipitating factor of convulsions. Thus the greater liability of first-born children to head injury during birth may be the cause of the greater incidence of epilepsy among them.

Epilepsy considered from the Mendelian Standpoint.

Davenport and Weeks (3) have attempted to show that epilepsy is due to the absence from the inherited germinal material of a unit character which behaves according to Mendelian laws. These authors have been fully dealt with by Myerson and the greater part of his refreshingly outspoken criticism appears to be entirely justified. It is difficult to take seriously conclusions which are based on the indiscriminate inclusion in the concept 'neuropathic taint' of chorea, paralysis, neurosis, alcoholism, epilepsy, feeble-mindedness, prostitution, and migraine, which here again exercises its usual fascination for the statistician of psychopathology. One point raised by Davenport and Weeks may, however, usefully be considered here. These authors state that 'when both parents are either epileptic or feeble-minded all their offspring are so likewise'. Epilepsy in both parents occurred only once in my own series; in this instance, in addition to the parents, the paternal grandmother and a paternal uncle were epileptic. There were four children of the marriage, all normal.

The main difficulty which is encountered by the attempt to investigate epilepsy on Mendelian lines arises out of the facts considered in the last section and their interpretation. Mendelian laws are concerned with the numerical proportions in which transmitted characters are manifested in the offspring. If a transmitted character depends upon the presence of an entirely fortuitous additional factor, e.g. trauma, before it can be manifested, clearly no uniformity can be expected in its manifestation, and hence no valid conclusions can be drawn concerning its mode of transmission. In many cases the inherited factor may be present without being manifested, as is possibly the case in the offspring of the two epileptic individuals just quoted. Only when there is available a method of detecting the latent predisposition to the disease will the application of Mendelian principles be practicable.

Summary.

1. In a series of 200 epileptics a family history of the disease has been found in 28 per cent., as compared with a figure probably under 10 per cent. in a control series from a hospital population.

2. A family history of the disease is obtained somewhat more frequently in the case of females than males.

3. The onset of the disease occurs in the first decade of life in a larger proportion of those with a family history of epilepsy than of those without such a history.

4. There was a history of early convulsions in the case of 28 per cent. of 176 epileptics. Early convulsions were almost twice as common in epileptics with a family history of the disease as in those with none.

5. Epileptics have been found to transmit the disease to about 1 in 20 of their offspring, but considering the probable error of the small numbers, little stress can be laid on this proportion.

6. The proportion of first-born among epileptics is twice as high, and of second-born children half as high again, as in the section of the population from which the patients were drawn. It is suggested that the increased liability of first-born children to receive cerebral injury at birth is a factor likely to be responsible for the increased proportion of first-born among epileptics.

7. The incidence of insanity among the relatives of epileptics was found to be no higher than in the general population.

8. The facts are held to indicate that a predisposition, which in at least 28 per cent. of cases is inherited, is an aetiological factor in epilepsy.

9. Our present knowledge is not sufficient to render practicable the application of Mendelian principles to the inheritance of epilepsy.

The present investigation forms part of a research into the aetiology of convulsive states conducted under the direction of Dr. George Riddoch. Its expenses have been defrayed by a grant from the Medical Research Council.

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THE SPASM OF TETANY CONSIDERED AS A DISTURBANCE OF THE PHYSIOLOGY OF MUSCLE¹

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DURING the last ten years innumerable papers have been written on the subject of tetany. Most of them have been concerned with the various ways in which tetany may be brought about and with the changes in the blood which may be associated with it rather than with the immediate mechanism by which the characteristic spasm of the disease is caused. It has generally been assumed that the spasm was due to some nervous disturbance, and the authors, if they have attacked the problem at all, have usually endeavoured to show that a particular blood change was capable of producing a state of hyperexcitability of the nervous system. The motor nerve-endings, the spinal cord, the cerebellum, have all been more or less indicted, yet, in spite of carefully devised experiments, there is no nervous mechanism to which the charge of producing the spasm has been brought home. The view put forward here is that the spasm is not nervous, but is due to a disturbance of the internal physiology of the muscles; there is some *a priori* evidence that the spasm is myogenous, and correlation of the normal chemical physiology of muscle with the chemical disturbances known to exist in the blood in tetany accords with this, and suggests that the immediate cause is a breaking-down of the contraction-producing substance of the muscles by chemical means, as in the veratrine contraction (24). It is believed that this view provides a satisfactory explanation of most of the muscular phenomena of the disease and is at least as worthy as the 'nervous' hypothesis of being considered in regard to their pathogenesis. A hyperexcitability of some portions of the nervous system undoubtedly exists in tetany (witness Hoffmann's sign), and it cannot be denied that a nervous impulse may be the exciting cause of the spasm, and that the normal nervous influence keeps the muscle in an excitable state; what is suggested here is that the muscles are liable to spasm because of an abnormal condition inherent in themselves and not because of any abnormal condition in the nerves or nervous system.

A priori Evidence that the Spasm is Myogenous.

It is needless to say that direct evidence of this kind is scant—otherwise the nature of the spasm would not remain in doubt. There are, however, some experimental and pathological findings and some indirect clinical evidence which require to be reviewed. It is to be presumed that a spasm must be myogenous if it is not neurogenous. MacCallum (9) showed, by perfusing one limb of a healthy

¹ Received December 17, 1925.

dog with blood from a parathyroidectomized animal, that the characteristic hyperexcitability of the muscles (or of the nerve-endings) could be produced while the central nervous system was not subject to any abnormal influences. From this and many other facts the part of the nervous system in tetany, if any, has been narrowed down to an abnormal sensitivity of the nerve-endings, and it is agreed that even this hypersensitivity is not due to nervous causes. That a spasm of nervous origin should be brought about merely from the more easy passage of the normal tonic impulses into a muscle is not a satisfactory hypothesis; nor is there any apparent reason why the resistance of the nerve-endings should, as a rule, be more reduced in the muscles of the extremities than elsewhere, nor why compression of the arm should reduce the resistance of the nerve-endings in the hand. Furthermore, even in cases of very prolonged tetany, no adequate changes have been found in the nervous system after death.

As long ago as 1884 Ringer (12) produced tonic spasms and muscular twitchings in frogs by the intraperitoneal injection of sodium bicarbonate and sodium phosphate, and he found that the spasmophilic state of the muscles persisted not only in an amputated limb but also when the nerve-endings were paralysed by curare. He deduced that the spasm was due to a poisoning of the muscles themselves and was independent, except for an exciting impulse, of all nervous influence. Paton, Findlay, and Watson (11) found in two of their experiments that it was possible for the nerve-endings in a limb of a parathyroidectomized cat to be paralysed by curare without any of the tetanic hyperexcitability to galvanism being lost; but in a number of their animals the curare affected not merely the nerve-endings but the muscle also, and the general sense of their findings was that the hyperexcitability was reduced. MacCallum (9) found that after curarization the muscles of parathyroidectomized dogs continued to be somewhat more excitable to galvanism than normal muscles, but he did not consider that the difference was sufficient to justify the conclusion that the abnormality of tetany was purely muscular; he makes no reference to a possible effect of curare of the muscle itself.

In certain rare cases of tetany in human adults (Hoffmann (6) and others) there has been extensive muscular wasting, and the anatomical changes found in the muscles in such cases have been of the kind associated with intrinsic muscular (myopathic) and not nervous disease (Schultze and Schiefferdecker (15), Schoenborn (13)).

Further, indirect clinical evidence is afforded by the close relationship between tetany and the undoubtedly myogenous spasm, myotonia, which indicates that both forms of spasm are due to similar causes and arise in the same structure.

Tetany is closely related to Myotonia.

The consanguinity of these spasms manifests itself (a) in the interchangeability of the two forms of spasm in occasional cases, (b) in the similarity of the spasms themselves, and (c) in the similarity of the non-muscular disturbances with which they are associated.

(a) In the case of myotonia atrophica which was under my observation in 1921 and 1922 there occurred, as well as the myotonia elicitable in the usual ways, spontaneous spasms indistinguishable from severe spasms of tetany. The patient was a woman of 39, and symptoms of myotonia atrophica had been present for two years before any spontaneous spasm came on. The spontaneous spasms affected at first only the right hand and forearm, later both hands and the right foot; they lasted often half an hour or an hour, and for a time became extremely frequent, occurring as often as twenty times a day. But the subsidiary diagnostic signs of tetany were not present. The occurrence of the converse condition—myotonia in cases of tetany—is better known. Hoffmann (7) recorded the case of a young man of 18 who had severe tetany beginning three days after an operation for goitre. The symptoms gradually subsided, and after about two months, when spontaneous spasms had almost ceased, myotonia could be elicited by strong voluntary contraction in the hand muscles, in the masseters, and in the muscles of the feet. Some muscles gave the typical myotonic contraction lasting as long as forty seconds when struck with the percussion hammer, and similar after-contractions occurred with electrical stimulation. The whole condition ended in complete recovery. A young man seen by v. Frankl-Hochwart (4) had a short attack of typical acute tetany; after a few days spontaneous spasms ceased, but when the patient closed his hand firmly he could only open it 'after rather a long time' (*erst nach längerer Zeit*); the signs of Chvostek, Erb, and Trousseau were still present. After a few days the myotonia passed off and the patient had no further symptoms. The cases recorded by Schultze (14), Kasperek (8), Bettmann (3), v. Voss (16), Orzechowski (10), and Schoenborn (13) are also to be mentioned; in all of them, except that of Bettmann, the myotonia passed off with the tetany. v. Frankl-Hochwart (5) found myotonic symptoms—spasms induced by strong voluntary contraction of certain muscles—as a residual symptom of tetany in 6 of the 37 cases on which his classical paper on the prognosis of tetany was based.

(b) Both the spasm of tetany and of myotonia are continuous (tonic) spasms; they affect most commonly the muscles of the hands, of the forearms, and of the feet, but they may affect any muscle; both, if intense, are painful; both may be excited by emotion. The main difference seen in the spasms themselves is that while that of tetany as a rule comes on spontaneously, myotonia usually requires that a contraction of the muscle it involves shall be evoked first. The general electrical hyperexcitability of the muscles that is associated with tetany is hardly to be expected with myotonia, on account of the myopathic changes that are present, but in both conditions an increased response to galvanism is found, and only in these two conditions are the 'opening' contractions obtained with ease.

(c) The non-muscular disturbances which occur both in tetany and in myotonia atrophica are chiefly those of ectodermal structures—cataract of the ocular lenses, changes in the skin, excessive sweating, changes in the hair and nails; but, in addition, psychical changes, dysmenorrhoea, and emaciation are common to both diseases. As regards metabolic disturbances, free creatine in the

urine is met with in both; whether the reduction of the calcium content of the blood which is so frequently found in tetany is a feature also of myotonia atrophica has not yet been determined, but apart from that it may be said that all the non-muscular symptoms met with in the one disease occur also in the other. It is in the highest degree unlikely that such a group of heterogeneous changes should not, in both cases, be due to the same underlying cause.

The spasms of tetany and of myotonia are probably not identical, but none of their known differences (spontaneity of onset, duration, electrical signs, and likelihood of recovery) are such as to suggest that they originate in different structures. The suggestion rather is that tetany affects temporarily a mechanism which in myotonia is more permanently, though less completely, upset.

There is cogent evidence that myotonia is of intrinsic muscular origin. Though usually brought about by strong voluntary contraction, the spasm is to be evoked also by electrical stimulation and by percussion of the muscle. Now, in the electrical stimulation of normal muscle, the electrical stimulus replaces the natural nervous stimulus, and when the stimulation ceases the contraction ceases also. But in the myotonic muscle the spasm continues, when nothing equivalent to nervous stimulation is occurring: no question of 'nervous after-discharge' can arise. This applies similarly when the spasm is provoked by a percussion stroke on the muscle. Percussion may, too, cause only the fibres that are actually struck to go into spasm. It is hardly possible to consider the spasm excited either by electricity or by percussion as a reflex, for reflexes as we know them are concerned with groups of muscles and with movements, not with individual muscles or fibres. It has been shown that during the spasm, after voluntary contraction has ceased, there is no action-current in the muscle (Adrian and Adie and Greenfield (1)), so that the spasm is at any rate not due to the same kind of nervous influence which brings about a voluntary contraction. Finally, myotonia, in the various diseases in which it is encountered, is always associated with structural abnormalities in the muscles, and even in cases in which the spasm has recurred for many years no changes in the nervous system have been found. The only explanation seems to be that the spasm is due to abnormal action within the muscle itself, and this is the view most widely adopted.

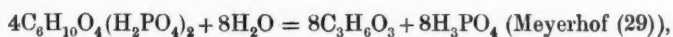
This adds to the probability that tetany also is due to a disturbance of the intrinsic action of the muscles.

The Chemical Physiology of Muscle.

Nothing was known until a few years ago of the mechanism which caused a muscle to contract, but the experimental work which has been going on for the last ten years is now rapidly reducing the whole action to terms of physics and chemistry.

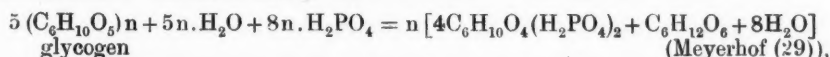
There are many ways by which a muscle isolated from the body can be made to contract (e.g. rigor mortis, heat rigor, veratrine, caffeine, quinine), and hence the contraction-producing influence results from something contained within the muscle itself and not directly from anything transmitted to it from the nervous

system. In whatever way the contraction is caused, lactic acid is set free and, according to Embden, phosphoric acid also is liberated, but is absorbed again. The generally accepted theory is that the acids set free, by virtue of the action of their free hydrogen ions on the contractile muscle-fibre, cause the latter to contract. Lactic and phosphoric acids are present within muscle in the form of a precursor to which the name 'lactacidogen' has been given. Lactacidogen has been shown by the freezing-point, optical properties, and phosphorus content of its osazone, and by much contributory evidence, to be hexose-diphosphoric acid (or diphosphate) and therefore it has the formula $C_6H_{10}O_4(H_2PO_4)_2$. This substance in the resting muscle is closely in contact with the contractile fibre, and by the motor nervous impulse its molecule is believed to be disrupted, and hydrolysis takes place, according to the formula



the lactic and phosphoric acids thus set free causing the fibre to contract.

Lactacidogen is derived from glycogen in combination with phosphoric acid, the equation evidently being



so that glycogen is the ultimate source of the energy of the muscular action. When, however, the lactic acid precursor is broken down, a large fraction of it is re-formed again from the constituents during the recovery of the muscle.

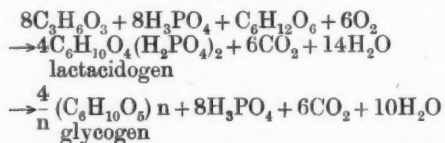
During *rest* the muscle exhibits, in a slight degree, exactly the same kind of chemical activity as takes place with much greater intensity during contraction.

Contraction. When a muscle contracts, lactic acid ($CH_3CHOH.COOH$) and phosphoric acid (H_3PO_4) can be obtained from it in equimolecular quantities, and the amount of lactacidogen [$C_6H_{10}O_4(H_2PO_4)_2$] (or glycogen) it contains is reduced (Embden and his co-workers (21)). Contraction is independent of the presence of oxygen and can go on for a considerable time in the absence of it. A. V. Hill (25) has shown that the amount of heat produced in contraction corresponds approximately to that evolved in the production of lactic acid from the equivalent amount of glycogen. The various parts of this combined process—reduction of the amount of lactacidogen (or glycogen), production of lactic acid, production of phosphoric acid, and the production of a corresponding amount of heat—have been shown to take place whether the muscular contraction be the result of nervous or electrical stimuli (Embden (22), Hill and Hartree (26), Meyerhof (29)), of rigor (Meyerhof (30)), Fletcher and Hopkins (13)), or of the chemical action of drugs (Riesser (31), Hartree and Hill (24)), so that it would appear that, no matter what the influence is by which lactacidogen (or glycogen) is broken down, contraction results.

Relaxation. Since a normal muscle relaxes immediately after a twitch or after the cessation of a nervous stimulus, it is apparent that the acids which cause the contraction must be quickly neutralized or withdrawn from contact with the contractile substance. It has been found that the rise in the hydrogen-

ion concentration in the muscle, even after prolonged activity, is very slight, and so it is evident that neutralization takes place within the muscle. The amount of alkaline phosphates and carbonates present in the muscle is, however, not sufficient immediately to absorb (buffer) all the acid produced, and it was suggested by Meyerhof (29), on thermo-dynamic arguments, that the proteins of the muscle acted as buffers in much the same way as haemoglobin acts as a buffer for H_2CO_3 in the blood. Some confirmation of this was given last year by Andrews, Beattie, and Milroy (18), who showed that when the colloids were filtered off from muscle-juice the buffering capacity (against H_3PO_4) was reduced by about half. Evidently, when the acid precursor is broken down, the acids formed act momentarily on the contractile fibre, and are almost immediately neutralized by the salts and protein of the muscle; relaxation then ensues: during a sustained contraction, molecules of acid are constantly being liberated, acting momentarily on the contractile substance and being quickly neutralized.

Recovery. It has been demonstrated by A. V. Hill (25) that the recovery process is not a mere removal of break-down products resulting from contraction, but is a positive process involving a large expenditure of heat (energy). Unlike the other processes outlined above, recovery is an oxidative process, and it requires a considerable time for its completion. The amount of O_2 absorbed and the amount of heat evolved during recovery prove that all the lactic acid is not removed by oxidation, but that four-fifths of it, with the phosphoric acid, is re-formed into its precursor, and the remaining one-fifth (or an equivalent amount of glycogen) is oxidized, and thus provides the chemical energy requisite for the synthesis. In this the results of direct analysis, of thermodynamical measurements, and of experiments by means of CO_2 and O_2 estimations on the human subject all agree. The equations given by Meyerhof (29) for the process of the re-formation of lactacidogen or of glycogen in this way are:



In the isolated frog's muscle recovery in oxygen after prolonged stimulation takes about five hours. In the human subject, by measuring the oxygen consumption, Hill and his pupils have found that recovery after violent exercise takes 60–80 minutes. Recovery proceeds rapidly in the time immediately after and also during contraction, reaches its height a few minutes after cessation, and then gradually decreases in rate.

Lactacidogen in muscle tends constantly to break down slowly, though under healthy conditions it is as quickly renewed. The rate of its decomposition is influenced by many factors, some of which are known.

Since the molecule is easily broken down, one surmised that even weak

alkalis would be capable of breaking off the H_2PO_4 groups, and that the consequence of the disruption would be the same as if it had been brought about by nervous influences. It has in fact been found by Emden and his co-workers (21, 27) that the break-down of lactacidogen in minced muscle is favoured by a decrease, and hindered by an increase, of the hydrogen-ion concentration of the surrounding medium, the rate of break-down in 2 per cent. Na_2CO_3 solution, for instance, being considerably greater than in water. Correspondingly, a muscle placed in an alkaline solution undergoes contraction.² Recently the Emden school has studied the influence of various ions on the rate of break-down of lactacidogen; among the anions studied (CSN' , I' , Cl' , tartrate, SO_4'' , citrate, succinate, F') those of iodine and chloride had a pronounced influence in hastening the break-down, while those of fluoride and, to a less extent, citrate not only prevented any break-down but actually caused a synthesis. This has been confirmed for fluoride by Andrews (17) at Belfast. Among the kations studied (Na^* , K^* , Ca^{**} , Ba^{**} , Mg^{**} , NH_4^*), none had any pronounced effect except barium and calcium, the action of the latter being by far the greater. Calcium not only inhibited the break-down of lactacidogen but greatly aided its synthesis, and its action was studied in some detail by Lange (27), to whose paper the reader must be referred. The curve of Fig. 1 has been drawn from the results of one of Lange's experiments, to show the relation between the inhibitory effect of Ca and its concentration at low concentrations. Glycogen is another substance whose presence greatly hinders the break-down and favours the synthesis of lactacidogen; it has been found that a 2 per cent. solution of glycogen or of wheat starch completely prevents the normal break-down in muscle broth, and the addition of even 0.1 per cent of glycogen has an effect in increasing the action of calcium (see Fig. 2).

Tetany.

If the spasm of tetany be myogenous, such are the findings at our disposal to explain it; the following, though not the only explanation they afford, appears to be the most direct.

The factors present in the human body which are known to have a definite effect in inhibiting the break-down of lactacidogen are: free hydrogen ions, calcium (approximately 10 mg. per cent. in blood-serum), glycogen, and the minute amount of fluoride present in muscle. On the contrary, alkalosis, deficiency of calcium, deficiency of fluoride, if it occurs, and to a less extent deficiency of glycogen will all tend to increase the break-down. Doubtless there are other factors yet to be discovered.

The break-down of the energy-releasing substance in living muscle denotes a tendency to contraction, and if the rate of katabolism be sufficient, contraction (spasm) will ensue. In tetany one or other or both of the two most important

² A muscle placed in acid—particularly a dilute, inorganic acid—also undergoes contraction, presumably because of the direct action of the acid on the contractile elements. (See, however, on this point, Meyerhof (29).)

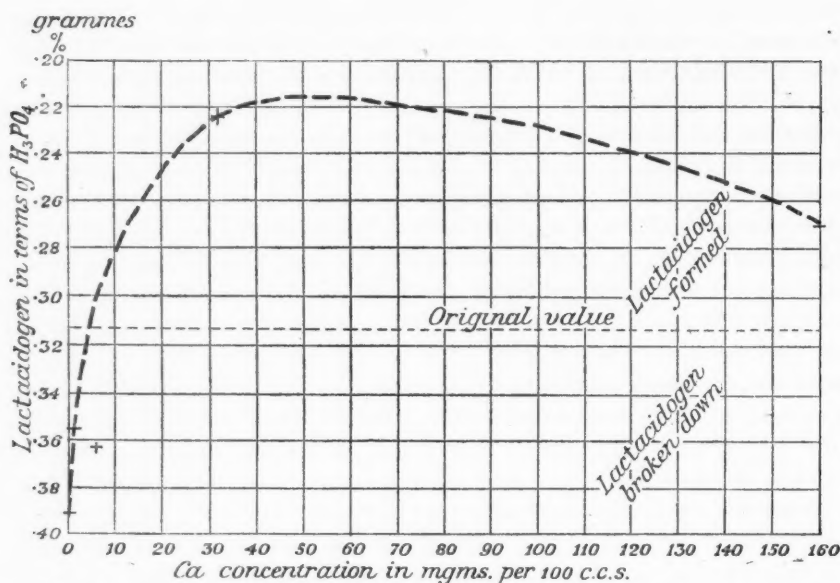


FIG. 1. Curve from results of Lange's Experiment 3, showing effect of small amounts of calcium in preventing the break-down and aiding the synthesis of lactacidogen; pieces of the same muscle were kept in different strengths of Ca solution for 4 hours at 11° C. The lactacidogen is estimated by the change in the amount of available H_3PO_4 .

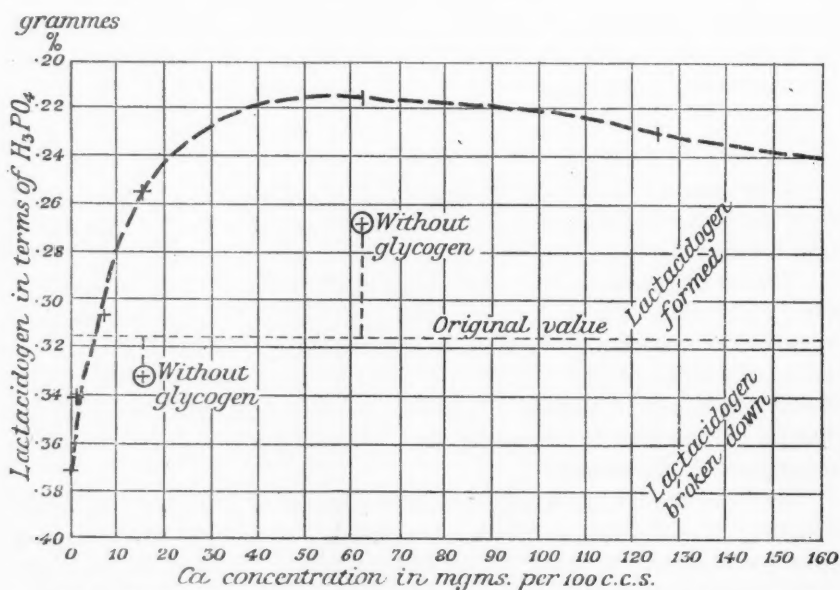


FIG. 2. Curve from results of Lange's Experiment 10; pieces of a muscle were kept in Ca solutions to which 0.1 per cent. glycogen had been added. The results of two of the controls without glycogen are shown.

factors in increasing this rate—deficiency of calcium and deficiency of hydrogen-ion concentration—are present. From Fig. 1 it is seen that the amount of calcium normally found in the blood (approximately 10 mg. per 100 c.c. of serum) has a great inhibitory effect on the disintegration of lactacidogen; but at that concentration the curve is very steep and a small reduction (say to 5 or 6 mg. per cent., such as is found in tetany) to a large extent removes this inhibitory effect. In Fig. 2, where the addition of glycogen has produced a closer approximation to living conditions, it is seen that the consequence of such a reduction in the calcium concentration is greater still—it takes away a large fraction of the power of counteracting the disintegrating influences.

Again, in tetany—or at least in many cases of tetany—there is a considerable degree of alkalosis; the pH of the blood is increased to, say, 7.6. Now, lactacidogen breaks down freely in water, and every variation to the alkaline side increases the rate of break-down, and therefore tends towards muscular spasm. It must not be forgotten, however, that the contractile fibre is surrounded by a membrane not easily permeable except when the muscle contracts, and the question may be raised whether the lactacidogen lying, as it is believed to lie, within this membrane is affected by the increased alkalinity of the surrounding medium. The answer to this is that in the isolated whole muscle veratrine, caffeine, and quinine all cause by chemical action a contraction with break-down of lactacidogen and a muscle placed in alkali undergoes contraction. Ringer's experiments mentioned above show that this effect is produced also on muscles in the living animal. All these results are in accordance with the view that the lactacidogen of muscle is accessible to chemical influences, and influenced by alkalosis of the blood percolating the muscle.

Whether these two factors are in themselves sufficient to produce the spasm of tetany or not, it is apparent that they must play a considerable part, and that the spasm is, if not entirely, at least in a great measure, attributable to intrinsic muscular disturbance resulting from them. Nervous hyperexcitability is admittedly present, and nervous influences probably help to increase the rate of disintegration, of lactacidogen.

Chvostek's sign and Erb's sign. In circumstances in which the energy-producing substance is less stable than normally, it is to be expected that stimulation of motor nerves will produce an exaggerated effect. To this cause Chvostek's sign may be attributed. The exaggerated effect of electrical stimuli is similarly explicable, and it is noteworthy that in tetany the increase of electrical excitability is more pronounced for direct stimulation of the muscle (galvanism) than for stimulation through the nerve (faradism). A state in which the effective acids are more easily released in the muscle affords therefore a rather better explanation of the electrical changes than a hyperexcitability of the nerve-endings.

Distribution of the spasm. The 'neurogenic' hypothesis fails to explain the characteristic distribution of the spasm in tetany, and it must be confessed that neither does the 'myogenic' hypothesis advanced here offer any immediate

explanation of it. But recent work suggests that its reason is likely to lie in differences in the properties of the muscles themselves—aided perhaps by factors of circulation and temperature. Muscles differ, for instance, in the amount of lactacidogen they contain and in their excitability, those of quick action having in both respects a superiority over those that are slower. It is noteworthy that in tetany it is small muscles—in the limbs, in the face, and in the larynx—that reveal the tendency to spasm most, and smallness is associated with fineness of structure.

It may be taken as almost certain that the muscular contraction of tetany, like all forms of contraction hitherto studied, involves a breaking down of lactacidogen (or glycogen). It does not seem possible at present to show definitely *by experiment* whether this break-down is due to chemical or to abnormal nervous influences. That the spasm is essentially myogenous is suggested by its relation to myotonia. There is, however, one observation on the human body which, if confirmed, would be almost conclusive. In the nineties of last century, when tetany was minutely studied, some fatal cases were reported in which the spasm had persisted unabated after death and passed without relaxation into rigor mortis (v. Frankl-Hochwart (4)). At death all nervous influences are presumably withdrawn from the muscle, and if the spasm be neurogenous, such persistence could hardly occur; if myogenous, persistence is to be expected in severe cases.

Summary.

There is some experimental and pathological and some indirect clinical evidence that the spasm of tetany is intrinsically muscular.

The chemical physiology of muscular action is outlined and the theory is put forward that the spasm of tetany is due to the breaking down by chemical influences of the lactacidogen (or glycogen) of the muscles involved.

Calcium has been shown by Lange to exert a strong influence in preventing the break-down of lactacidogen, and, at the concentration of calcium present in the blood, a small reduction removes a great deal of this inhibitory influence.

Lactacidogen breaks down more easily when the hydrogen-ion concentration is reduced; the effects of alkalosis in helping to cause tetany and of acidosis in relieving it may be thus explained.

The same hypothesis affords satisfactory explanations of the signs of Chvostek and Erb.

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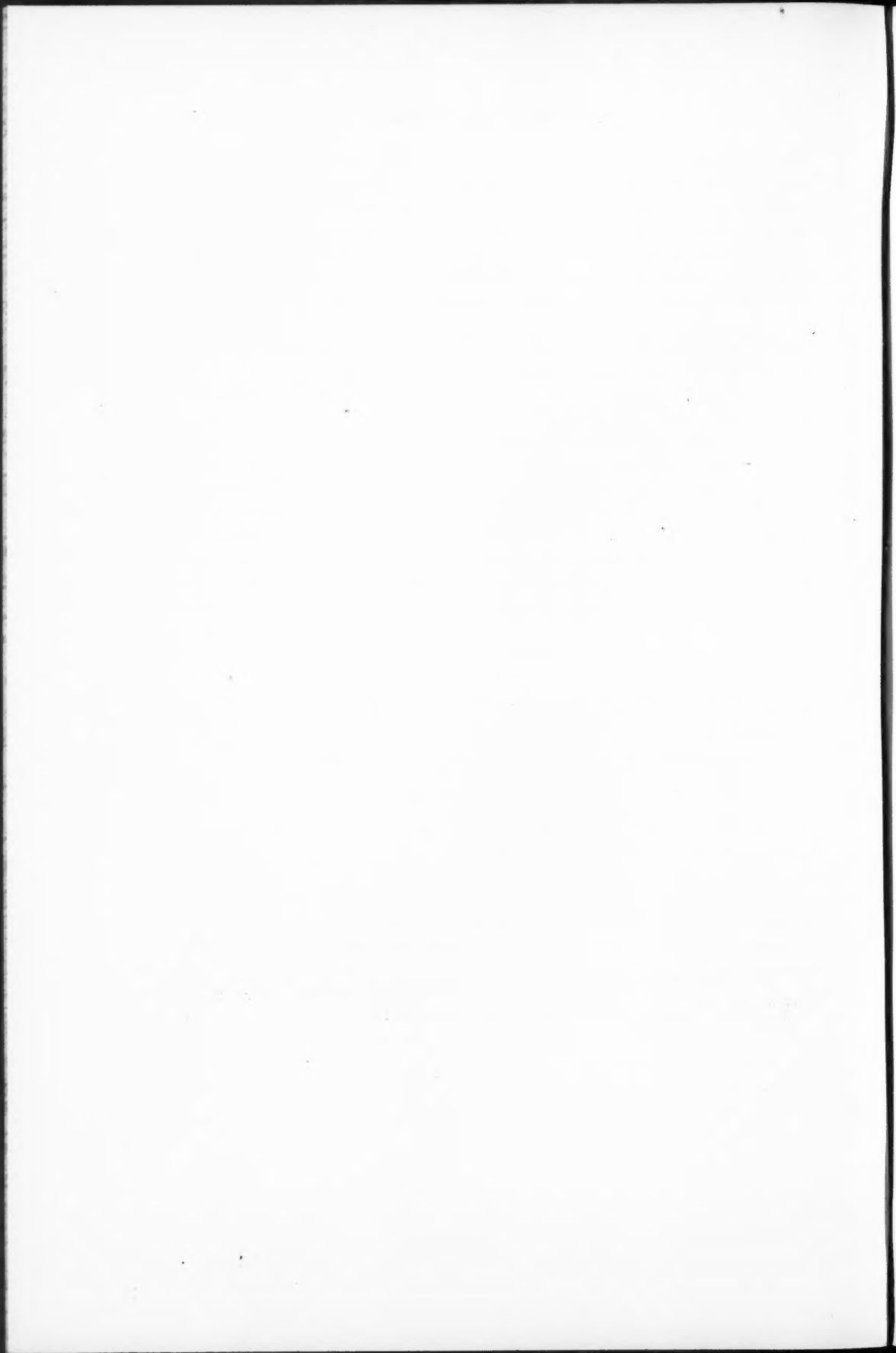
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EARLY ACCOUNTS OF ACHOLURIC JAUNDICE AND THE SUBSEQUENT HISTORY OF WILSON'S PATIENTS¹

By J. M. H. CAMPBELL²

NEARLY thirty-five years ago Claude Wilson described six members of a family as having 'a hereditary condition in which an enlarged spleen is accompanied by a sallow or subicteric complexion' (1), and in a second paper with Stanley three years later 'a pronounced corpuscular anaemia for which no doubt the splenic disease is responsible'. Through his introduction I have been able to bring up to date this family history and to examine the only survivor of these six patients.

The diminished resistance of his red cells to haemolysis by hypotonic saline, and the presence of bile-pigment in the blood but not in the urine, confirmed the diagnosis of acholuric familial jaundice. As this is better known through the descriptions of Hayem (3) and Minkowski (4), I propose here to give the salient points of Wilson's two papers, to describe rather more fully the findings in the present patient, and to add a very short history of our knowledge of this disease.

Wilson's Family with Large Spleens and Subicteric Complexions.

The first patient, Mrs. A. P., was born in 1825 and was said to be a healthy girl with an unusually fresh and beautiful complexion. There was no history of any similar trouble among her family, who were in comfortable circumstances. She married in 1850 and went to live at Tunbridge Wells, and the following year, shortly before the birth of her daughter, had an attack of some sort of jaundice, after which she was always sallow. Seven years later she and her two eldest children were seen by Sir William Gull, who said they probably had ague cake, from catching malaria at Worthing. Mrs. A. P. remained in fair health till she was 60, but towards the end of her life her spleen projected three inches below the costal margin and the liver was slightly enlarged. She was anaemic and had an icteric tinge of the skin and conjunctivae, but the urine was normal.

Of her six children who grew up two have already been mentioned as suffering from enlarged spleens. Three showed no signs of the family disease,

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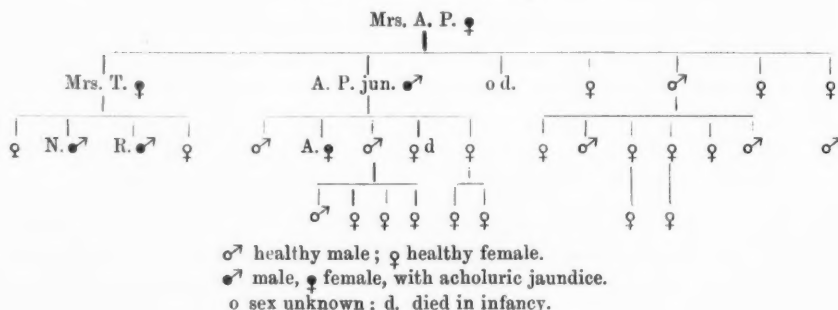
[Q. J. M., April, 1926.]

while the fourth was rather sallow and once had an attack of jaundice after a chill, but her spleen was not enlarged and she was in good health when 68 years old.

Mrs. T., her eldest daughter, was sallow and had a large spleen before she was 7, but in spite of this her health was generally good. Later she had periodical attacks of epigastric pain with chilliness, vomiting, and decided jaundice, in one of which she passed a gall-stone, so that probably all these exacerbations could be attributed to the passage of small biliary concretions. The spleen was very large and her eyes were seldom free from a trace of icterus. She had four children and died when 40, deeply jaundiced and very anaemic, shortly after giving birth to a still-born child.

Post-mortem, the spleen weighed about two pounds and was firm with a thickened capsule; there were no infarcts, and the Malpighian corpuscles were not prominent. The microscope showed dilated sinuses, general engorgement with blood corpuscles, minute haemorrhages, and some fibrosis. The liver was enlarged and section showed dilated capillaries without any apparent increase on connective tissue. There were many cells containing fat globules and a golden brown pigment. Unfortunately, owing to the very hurried conditions under which the post-mortem was permitted, the gall-bladder was forgotten. The kidneys were normal and there were no enlarged lymph glands.

TABLE I. *Genealogical Tree of Wilson's Family with Acholuric Jaundice (with recent additions).*



Her brother, A. P. junior, developed the condition before he was 5 years old. He was always sallow, but throughout life was liable to 'bilious attacks', when he became jaundiced with bile-pigments in the urine. The spleen was greatly enlarged and on two occasions his haemoglobin was between 50 and 60 per cent.

In the next generation at least three members were affected—N. and R., the two sons of Mrs. T., and her niece A., a daughter of A. P. junior. A. was yellow soon after birth, and when she was examined as a girl the spleen was enlarged and her haemoglobin was 60 per cent. In spite of this she was not at first much troubled with symptoms. She married and went to India, where she became worse and died in 1914, aged 32, of '? pernicious anaemia'. Her only child was still-born.

Her cousins N. and R. were yellow when a few months old, and as boys their spleens were much enlarged and they were always troubled with symptoms. N. died in 1922 of 'acute anaemia', aged 42, but R. improved and came to me for examination recently.

There have been, so far, no cases in the fourth generation. Though A., N., and R. all married, they had no living children, but the healthy members of this generation have had ten children. Of these ten, and of the members of the second and third generations not already mentioned, some were healthy and some delicate, but none had any definite evidence of the family disease. One or two were rather sallow with a tendency to anaemia, and may have been slight examples of the disease, but there was no opportunity to make an examination of their blood.

Wilson's speculations in the first paper, before he had made a post-mortem examination, have been more widely quoted than the very accurate conclusions in the second paper.

The first paper ended thus: 'As to the nature of the morbid condition present, I must confess to being quite in the dark. Many points suggest malaria, though in no case have we typical attacks. As all known forms of splenic enlargement except this may be excluded, we seem thrown back on to regarding it as a true hereditary malarial taint or something of a different nature of which we at present know nothing. The more I see and think of these cases the less do they remind me of malaria.'

The conclusions to the second paper were much more definite. 'It remains to consider how far we are justified in modifying our previous estimate of the true nature of these cases. . . . Since then we have become possessed of further knowledge both of these patients and of the functions of the spleen. Firstly, there is a pronounced corpuscular anaemia, and no doubt can be entertained that the splenic disease is accountable for this. Secondly, in the light of recent knowledge of the functions of the spleen (Hunter, 'Physiology and Pathology of Blood Destruction', *Lancet*, ii, 1892, p. 1209), the last illness of Mrs. T. and the pathological appearances discovered point to her death being due to a rapidly progressing anaemia, dependent upon an active haemolysis of splenic origin. We consider that the attacks from which A. P. junior has so often suffered, accompanied by fever, engorgement of the spleen and liver, and highly coloured urine, also point to short periods of active destruction of red blood corpuscles, whether the pigmentation be due to bile or not.'

Wilson was now convinced that it was not malaria, as, in addition to the history and clinical features, all the blood examinations had failed to reveal any parasites, and he discussed its relationship to the cases described as splenic anaemia.

From these cases practically all the clinical points about acholuric jaundice had been realized—the great enlargement of the spleen with perhaps a slight enlargement of the liver, the icteric tinge of the skin and conjunctivae with the urine normal, the tendency to anaemia and to periodic attacks of true jaundice

with biliary colic, and the inheritance of a disease which was generally chronic though compatible with long life. Little remained to be added except the proof that the yellow colour was due to bile-pigment in the plasma, that the urine contained urobilin though not bile-pigments, and that the red corpuscles were abnormally fragile to some haemolytic agents.

Fragility of the Red Cells and other Tests in one of these Patients.

I have had the opportunity of examining R., who was the son of Mrs. T. and the grandson of Mrs. A. P. He was yellow when three months old, and before he was 10 his spleen projected two inches below the costal margin. He was very susceptible to cold, and his mother stated that a cold bath always turned him the colour of a daffodil. He was generally rather better when taking arsenic, and the febrile attacks to which he was very subject seemed to be less frequent. But although the general health improved with treatment, three years later the spleen was larger. The urine was a deep amber colour and contained no albumin or sugar. The red corpuscles numbered 3,150,000 and the white 5,000 per c.mm.

On growing up, the exacerbations became less frequent, and though he was practically always yellow and rather anaemic he was able to follow a fairly active occupation and regularly played tennis. He had some symptoms of gall-stones in 1915, but this trouble passed off without operation. When examined recently he was 44 years old, rather short and stout, but with a healthy complexion in spite of his yellow colour. I was surprised to see any one feeling well and doing his ordinary work so yellow; the colour was certainly deeper than in most patients with acholuric jaundice except during their periodic relapses.

The plasma was the same deep colour and contained bile-pigment, giving an indirect Van den Bergh test. The urine contained urobilin but no bile-pigment. His red cells were tested with various strengths of sodium chloride, and haemolysis started with 0.6, was considerable with 0.54, nearly complete with 0.48, and complete with 0.45 per cent. NaCl; compared with the normal control which started at 0.45 and was nearly complete with 0.39 per cent. NaCl.

The healthy appearance was partly due to the absence of any severe anaemia (his haemoglobin percentage was 80) and partly to a rather bronzed complexion which made the yellow colour less obvious in the face than elsewhere. The spleen was very large, projecting more than four inches below the costal margin, and the notch could easily be felt; it was not tender, but he had recently had a dragging pain there after any rather vigorous games of tennis. The physical examination revealed no other abnormalities, and he had not missed his work for illness for many years except during the influenza epidemic. In many ways this is a very typical case of acholuric jaundice, the interference with health being less than would be expected considering the greatly increased rate of destruction of the red cells.

Since seeing this patient I find that Hutchison and Panton had followed up the family in which cases had been recorded earlier by Moxon and Murchison (7).

As they found the typical blood changes of acholuric jaundice in a descendant, there can be no doubt of the diagnosis. But the description gave few of the characteristic features and could hardly have been recognized, as there was no mention of enlargement of the spleen and the patients were said to have been always jaundiced, the urine containing bile-pigment. On the other hand, in Wilson's cases the spleen was a very prominent feature, and though he did not state that the plasma contained bile-pigment and the urine did not, he recognized that while the patient was still yellow the urine was generally free from bile-pigment, though from time to time during exacerbations it was present. Presumably it was at this stage that Hutchison examined his patients.

Hayem's Acquired Cases.

In France attention was first drawn to this disease in 1897 by Le Gendre (9) showing a young man, who had been yellow for twelve years with urobilin but no bile-pigment in the urine. In its chronic but benign course with exacerbations the case was typical, but he did not refer to the enlarged spleen or the anaemia. After his paper Hayem (10) referred to a patient whom he showed at the following meeting, describing the presence of bile-pigment in the plasma while it was absent from the urine.

The following year Hayem produced his classical papers (3, 10), and after describing various types of chronic jaundice he continued: 'Parmi celles-ci je vous signalerai l'ictère chronique très particulier de certains dyspeptiques, qui se traduit par une coloration jaune chamois des téguments, et notamment de la paume des mains. Cet ictère a surtout comme caractère spécial l'absence de pigment biliaire dans les urines, alors que le sérum sanguin donne nettement la réaction de Gmelin. J'en ai observé plusieurs exemples.'

An excellent description of five cases followed, and though they are generally regarded as examples of the acquired type, certainly one and possibly two had some relatives with chronic subicterus. His summary of the common features of these five cases only differed from modern views in the stress he laid on their digestive disorders, for which several had originally consulted him. 'De l'étude de ces faits se dégage nettement la conception d'une maladie particulière caractérisée essentiellement par un ictère chronique d'une durée indéfinie avec poussées paroxystiques passagères; une hypertrophie lisse et modérée du foie; une tuméfaction plus marquée de la rate avec sclérose progressive; des troubles digestifs et une anémie assez intense peuvent à certains moments atteindre un très haut degré.'

Hayem then reviewed various possible explanations, and after adequate discussion dismissed biliary obstruction, though he was aware that some of the patients suffered from this from time to time as a complication; he also dismissed hypertrophic biliary cirrhosis, as although the liver was often involved there were few or none of the classical signs of cirrhosis. His final suggestions are best given in his own words: 'Supposez un ictère infectieux assez bénin

pour ne pas être fébrile; supposez que cet ictère soit un ictère à rechute, que le nombre des rechutes soit indéfini, et qu'entre les poussées aiguës il persiste à la fois de l'ictère et une grosse rate indiquant la persistance de l'infection, vous aurez la maladie dont nous cherchons à préciser la nature.'

'Je vous propose de l'appeler ictère infectieux chronique splénomégalique à formes paroxystiques.' 'Tous mes malades avaient une gastrite parenchymateuse. C'est l'état habituel dans l'ictère catarrhal. Le duodénum participe à l'inflammation gastrique et de là les lésions remontent dans les voies biliaires.'

This is an excellent description of the clinical features, including the large spleen and the anaemia, but in trying to understand the cause sufficient importance was not attached to these two features. Hayem, like most of the other early French writers, looked on it as mainly a disorder of the liver, while Wilson had already realized that the anaemia, yellow colour, and periodic exacerbations were due to haemolysis of splenic origin. Apart from his general service in drawing attention to this condition, Hayem has the credit of proving the presence of bile-pigment in the plasma, while it was absent from the urine.

Shortly after, a large number of cases occurring in several families were described by Gilbert and his pupils (11), who discussed the large spleen and the anaemia and found that in many of the patients the plasma contained bile-pigments while the urine did not. These cases have not always been recognized, probably because they were rather a heterogeneous collection of various types of jaundice and even sallowness, so that, unlike every one else, they stated 'l'ictère acholurique est d'une remarquable fréquence'.

Apart from cases of biliary cirrhosis and gall-stones, many seem to have been what used to be called 'xanthochromie', but several were typical acholuric jaundice.

Minkowski's Familial Cases.

In 1902 Minkowski gave his classical description of the disease at a Congress at Wiesbaden (4). This is a short but excellent paper describing a family where there were eight cases in three generations. He described the large spleen, the yellow colour of the skin, and the urine containing excess of urobilin but no bile-pigment. His patient died of double pneumonia, and post-mortem there was no cirrhosis and the structural changes in the liver were not more than could be accounted for by the pneumonia, but there were pigment stones in the gall-bladder. The spleen, which weighed 1 kgm., was hyperplastic and hyperaemic, and an iron reaction was given by the kidneys. As in Wilson's cases, malaria was discussed but excluded.

Minkowski says: 'Es handelt sich vielmehr um eine ganz eigenthümliche angeborene Affection, die unter dem Bilde eines lebenslänglichen Icterus mit andauernder Urobilinurie, Milzhypertrophie und Siderosis der Nieren einhergeht, evident auf einer hereditären Anlage beruht und die Lebensdauer nicht zu verkürzen scheint. Die Affection kann im Einzelfalle leicht zur Diagnose einer Lebercirrhose Anlass geben. Alles scheint darauf hinzudeuten, dass dieser

Affection eine besondere Anomalie in dem Umsatze des Blutpigmentes—vielleicht als Folge einer primären Veränderung in der Milz—zu Grunde liegt. Welcher Art aber diese Anomalie ist, kann vorläufig noch nicht entschieden werden. Es würde mich freuen wenn auf Grund dieser Mittheilung bald ähnliche Beobachtungen von anderer Seite beigebracht werden sollten.'

'We are concerned rather with a peculiar inborn affection which is characterized by permanent jaundice, the continued presence of urobilin in the urine, hyperplasia of the spleen, and an increased amount of iron in the kidneys. It is evidently hereditary in origin and does not appear to affect length of life. The condition may in an individual case easily give rise to a diagnosis of cirrhosis of the liver. Everything appears to point to the fact that it is caused by a peculiar anomaly in the exchange of the blood-pigment, probably as a result of primary change in the spleen. But what this anomaly is cannot for the present be explained. It would give me much pleasure if as the result of this communication similar observations should be quoted from other quarters.'

This paper gave another excellent clinical picture of acholuric jaundice and the post-mortem findings agreed closely with those of Wilson. Minkowski added the valuable fact of the increased amount of iron in the kidneys, but it is not clear if he regarded this as evidence of haemolysis.

An acquired non-familial case of acholuric jaundice was described by Bettmann (12), who was familiar with Hayem's work. He recognized the anaemia and tested the fragility of the red cells by Hamburger's method, but did not find any abnormality. The main interest of his paper is that he produced haemoglobinaemia and haemoglobinuria in his patient by exposure to cold. Other early papers in German were by Pick (19) and Krannhals (20), who collected all the cases he could from the literature and described a fresh family in which there were nine patients with acholuric jaundice and only three whom he saw without.

In England little interest seems to have been aroused by Wilson's description, and the first confirmation was by Barlow and Batty Shaw (15) in 1902, in their paper on 'Inheritance of Recurrent Attacks of Jaundice with Hepato-splenomegaly'. Barlow had seen some of Wilson's cases and recognized that the family he described suffered from the same condition. In 1903 Arkwright (17) described another family in Edinburgh, and Cocking (18) one in Sheffield.

Further cases were described in France by Chauffard (13) and Widal and Ravaut (14). It is clear that in England, France, and Germany the disease was independently described, and as soon as this had been done it was widely recognized by clinicians. It is interesting to see the very close agreement in many points in the papers of Wilson, Hayem, and Minkowski. Acholuric family jaundice produces such a striking clinical picture, and, except for some anomalous acquired cases, one patient resembles another so closely, that it is curious it was not earlier recognized.

Chauffard's Discovery of the Increased Fragility of the Red Cells.

About this time the whole subject of the haemolysis of the red cells with hypotonic saline was discussed by Ribierre (16), but, presumably owing to its relative rarity, he did not examine any cases of acholuric jaundice. Widal and Ravaut (14) examined in a single case the resistance of the red cells to haemolysis by hypotonic saline, using the recently described method of Vaquez and Ribierre. Unluckily, like Bettmann, they missed the changes, probably because they only examined an 'acquired' case (see later). In this paper they referred to an isolated observation by Schachmanin in his Thèse de Paris, 1887, of a man aged 51, in good health, who had been yellow for several years without bile-pigments in his urine, and in whom the liver and spleen were both enlarged.

It was not till five years later that this question of the fragility of the red cells was examined by Chauffard (5), who described this striking peculiarity in one of the classics dealing with this disease. From various other types of enduring jaundice he distinguished those in which it was acholuric, and recognized clearly that here the liver was not at fault, but that the disorder was due to haemolysis. He saw a condition compatible with long life and moderate health: 'La malade prudente refusa l'opération qu'on lui proposa et aima mieux garder son ictere, avec lequel elle faisait en somme depuis cinquante ans un assez bon ménage.'

Chauffard showed that the resistance of the red cells against haemolysis by hypotonic saline was decreased, contrary to what was found in ordinary jaundice, and concluded rightly that the discovery proved the haemolytic nature of acholuric jaundice—'peut-être après cette enquête clinique et hématologique la cause de la théorie hémolytique pouvait-elle être considérée comme gagnée'. In the three cases examined by him haemolysis started at 0.62, 0.66, and 0.52 per cent. NaCl, instead of 0.42 in the normal and 0.36 in ordinary jaundice, and there was less change in the point at which haemolysis was complete, so that the range, i.e. the variation among the different cells, was greater than normal. He described the smaller size and the reticulated nature of a large proportion of the red cells (27). The following year Dudgeon and Hawkins (25) also found this change in the fragility.

An enormous amount of work was done in France at this time on the fragility of the red corpuscles, and the 1907 volume of the *Société Médicale des Hôpitaux de Paris* contained five long papers on the subject (22) (23) (24). The most important discovery of Chauffard has already been described, and he also found that the abnormality was in the red cells and not in the plasma. Up to this time the French clinicians seem to have looked on the disease mainly as a disorder of the liver, and were puzzled to account for its acholuric nature, but they now realized the importance of the destruction of the red cells from Chauffard's discovery of their fragility. Widal (6) showed that after they had been separated from their own plasma the red cells were still more easily haemolysed, and that in the hereditary cases the fragility was greater than in the acquired, so

that sometimes, if whole blood only was used, the change in the fragility might be missed in these. This smaller change in the acquired than in the congenital cases has sometimes been confirmed, but much difference is not always found. Widal agreed with Chauffard's finding that the red cells were smaller in the familial type, but found that they were larger than normal in the acquired type.

The next discovery of importance was the great improvement which follows removal of the spleen. Micheli (28) in 1911 reported a successful case, and the following year Banti (29) published an account of a patient whose spleen he had removed in 1903. About this time Springthorpe and Stirling (21) in Australia reported the removal of large spleens from several members of a family, but it is not clear if these were really cases of acholuric jaundice, or some other form of family splenomegaly. Later some old successful cases were recognized, in which at the time it had not been possible to make a diagnosis; thus Dawson (30) reported a case in which the spleen had been removed by Spencer Wells in 1887, and Bland Sutton (8) another on which he had operated in 1895. In the former family a father and two children were affected, and in the one whose spleen was removed Dawson found that the fragility was not normal more than twenty years later. A single fatal case reported by Vaquez (24) in 1907, when much attention was focussed on this condition, had a great effect in prejudicing against operation, but after 1911 it became increasingly frequent.

Apart from these few papers on the results of splenectomy I have not followed the literature of the disease farther than Chauffard's discovery of the increased fragility of the red blood corpuscles. Excellent reviews of our present knowledge have recently appeared by Tileston (31) in English, and by Meulengracht (32) of Copenhagen in German. The latter is particularly complete, and in addition to thirty-three cases of his own he gives references to more than three hundred papers.

I wish to thank Dr. Claude Wilson for putting me in touch with his former patients and for providing me with their more recent family tree, and Mr. R. T. for coming to see me and allowing me to take his blood for examination.

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[Q. J. M., April, 1926.]

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HEREDITY IN ACHOLURIC JAUNDICE¹BY J. M. H. CAMPBELL² AND E. C. WARNER

THE inheritance of human qualities is of far-reaching interest to physicians and biologists, quite apart from its importance to those more directly concerned.

In a family which was described five years ago by one of us (38) there were several living members with acholuric jaundice, and others who had probably had the disease. In three the symptoms were sufficiently serious to make removal of the spleen desirable, and more than two years after this operation the results are so good that we have learnt more of their family history, and have been able to examine many of their kindred. There are others with acholuric jaundice, but first we wish to describe some of those apparently free from the disease (especially a brother and sister, of the oldest generation, Mr. K. and Mrs. P.), and secondly to consider the effect which such latent cases have on our views of its inheritance and pathology.

Mr. K.'s mother, who died before much was known about the disease, almost certainly had it, for she was yellow for many years, and the disease appeared in numerous descendants. His grandmother also had jaundice of some sort during the later part of her life, and her spleen was said to be enlarged (see Appendix).

Some Partial and Latent Cases of Acholuric Jaundice.

Mr. K. himself is nearly 60 years old, and has worked all his life as a stoker in a factory. He has hardly been away from work for more than a day or two at a time, and has kept the same strenuous job for twenty-five years. His wife says he has sometimes been sallow, but never yellow like two of the children, and she is a good observer who distinguishes clearly between the acholuric jaundice of two of her children and an ordinary attack of jaundice, from which one of the others had suffered. In 1921 he did not appear yellow or anaemic, and though his abdomen was difficult to examine, no enlargement of the spleen could be made out. He had no history of anything like the usual 'crises' of this disease, and regarded himself, with good reason, as an extremely fit working-man.

In 1925 these points were confirmed, and his blood was examined to prove that the disease could be transmitted through a healthy subject. The haemoglobin was over 80 per cent., but we were surprised to find that the resistance of

¹ Received December 22, 1925.

² Working under the tenure of a Beit Memorial Research Fellowship.

his red corpuscles against haemolysis by sodium chloride was diminished just as much as in a well-marked case of acholuric jaundice. As the blood had been carried some way in a tram, we thought some mechanical haemolysis might possibly have taken place, and arranged for him to come to hospital, where the blood could be taken under more satisfactory conditions and examined at once, but the result was almost the same (see Table I). His plasma contained bile-pigment, though not in great quantity, and his urine contained an abnormal amount of urobilin.

Clinically, it was impossible to diagnose acholuric jaundice, but the urine and plasma showed that slight haemolysis was taking place, and the red blood corpuscles showed typical changes.

Mr. K. had two brothers and two sisters. Of the two brothers and their ten children none had any signs of the family disease, and in the three whose blood was examined the red cells showed normal resistance against haemolysis.

Of the two sisters, one died of what was probably acholuric jaundice (see Appendix); the other, Mrs. P., was said to be healthy, but from the history of her children and from what had been found of Mr. K., it seemed that she, too, probably had the disease. She is now 60 years old, and, until recently, when she has had some oedema of her legs and shortness of breath, has always felt well. She had a very faint yellowish tint, but the doctor who was then attending her after a fall downstairs had made no comment on it, and it had not been sufficient to attract the attention of any doctor on her frequent visits to hospital to see her children. She did not appear anaemic, but though her abdominal wall was very fat, the spleen was easily palpable six inches below the costal margin. She had no history of anything resembling the usual 'crises', but when her blood was examined the resistance to haemolysis was just as much diminished as in typical acholuric jaundice (see Table I). Her plasma contained bile-pigment, and there was urobilin even in a very dilute specimen of her urine, the dark colour of which she had noticed all her life.

Mr. K. had twelve children, of whom three have acholuric jaundice—Nelly, Harry, and Albert. Mrs. P. also had twelve children, of whom three died young of what was almost certainly acholuric jaundice, and three others—Walter, Elsie, and Ethel—still suffer from it.

These eight, who are now alive, have all been examined, and the main facts about them are given in Table I. Elsie, Nelly, and Albert have had splenectomy performed, and are now in good health (50). This may be desirable in the case of Ethel, who has only just come under observation, but does not seem called for in any of the others. All these patients will be fully described in the Appendix, but one member of this fourth generation will be described here as there are certain points of special interest about him.

Harry K., who was 18 years old in 1921, looked rather delicate and anaemic, and his spleen was palpable two inches below the costal margin, but he had never been yellow and did not wish to have his blood examined. Four years later he seemed about the same, but had been able to be at quite strenuous work during

TABLE I. Showing the Condition of the Eight Living Members of the Family with Acoholic Jaundice and the Condition of Three Two Years or more after Operation.

[illegible]

* B. denotes van den Berg's test.

**** The symbols in column 8 have the following significance:**

++++ Haemolysis nearly complete; generally more than 85 per cent.

+++ Partial haemolysis; generally 50-80 per cent.

+ Partial haemolysis; generally 25-50 per cent.

(+) Slight haemolysis; generally less than 25 per cent.

((+)) Very slight haemolysis; about 5 per cent.

+ F. denotes Fouchet's test.

this time. The spleen was the same size, the haemoglobin percentage only 73, the red cells showed abnormal fragility, and the urine just gave a spectrum of urobilin. But there was no obvious yellow colour of the skin, though in the fold of the elbow and over the abdomen it was perhaps a little more yellow than normal, and the plasma contained a little bile-pigment.

All these three patients, without obvious acholuric jaundice, Mr. K., Mrs. P., and Harry K., have some abnormal haemolysis, as shown by the haemoglobin a little below normal, the bile-pigment in the plasma, and the urobilin in the urine; but in Mrs. P. the disease was not, and in Mr. K. it could not have been, recognized without examination of the blood, so that in studying the inheritance such patients would generally be missed.

Mr. K. and Mrs. P. were the only two patients we knew who, themselves without symptoms of the disease, appeared to have transmitted it. That they really had a modified form of the disease simplifies the question of its inheritance.

It is well recognized that, in the familial type of the disease, while many cases are congenital, others develop during childhood and early adult life, often after some acute illness, but it is not generally realized that some subjects may have the necessary basis for developing the disease without ever showing it at all.

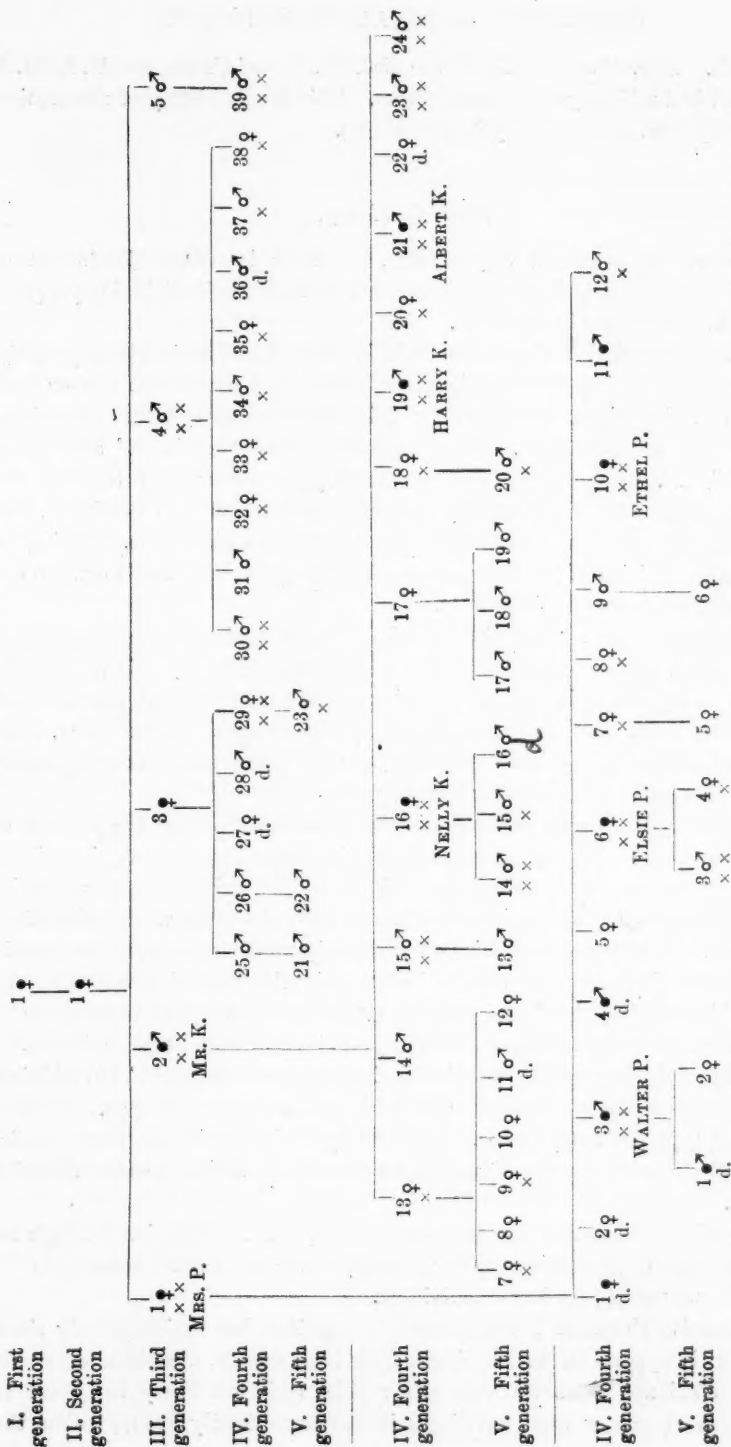
The family tree is given here. The single known member of each of the first two generations probably had acholuric jaundice. In the third generation there were two healthy sons, a daughter who probably died of it, and a son and daughter still alive, who have typical changes in the blood with little or nothing in the way of signs. In the fourth generation there are five members with typical acholuric jaundice, one with the disease in a partial form, and three who died young as the result of it, as well as a large number of healthy members. In the fifth generation few of the children have passed the age after which they cease to be likely to develop acholuric jaundice and the blood has not been examined in many cases, but one child almost certainly died of the disease. He makes the fifteenth member of the family who suffered from acholuric jaundice.

There are one or two general points about the family which seem worth mentioning. Apart from those dying in infancy the family appears to be long lived, with the exceptions mentioned below. There is no evidence that tuberculosis was present in any member living or dead. There is no evidence of syphilis in any member, and in the only four whose blood was examined the Wassermann reaction was negative.

On the other hand, there are three members with mitral stenosis, all of whom died relatively young, one (IV. 3) of heart disease at 18, one (IV. 14) of 'empyema, jaundice, and mitral stenosis' at 19, and one (III. 3) of what was probably acholuric jaundice at 33.

As regards the second it is possible, but not very likely, that the cirrhosis of the liver was some associated disease. Eppinger (25a) has described such an association, but generally the liver is found normal *post mortem*, except for increased pigment deposit, the iron reaction, and increased phagocytosis of the red corpuscles by the Kupffer cells. There may be some enlargement noticeable

TABLE II. Family Tree of Acholuric Jaundice in Five Generations.



Explanation.

(11) Each subject is denoted by a Roman and an Arabic figure, the former giving his generation and the latter his number in that generation, e.g. IV. 16. This number is used in Appendix I and throughout the text for all the subjects except the eight with scholastic jaundice referred to in Table I. The names of these eight are given above and are used in the text.

(2) ♂ male and female with acholuric jaundice; ♂ male and female free from acholuric jaundice.

(3) \times denotes those examined by the authors (35); $\times \times$ denotes those who have been seen and have had their blood examined (17); d. denotes those who died in infancy.

(4) There were no consanguineous marriages.

during life. As well as these three who died, IV. 33 had chorea, and II. 1, III. 1, and IV. 34 had a history of rheumatic fever. This family history of rheumatism has recently been considered by Lawrence (40).

Mendel's Theory.

This will be described very shortly, but those interested should consult Bateson's book (18), which contains a translation of Mendel's original paper (1) in addition to much other information.

Mendel showed that characters could be isolated and dealt with separately, each being present singly or doubly according as they come from one or both parents, and that these characters (or units of inheritance) were transmitted independently of each other. Some characters were 'dominant' and others 'recessive', i. e. when one of each of these types were mixed together the individual only showed somatically the character which was dominant, but genetically the germ-cells contained equally the two characters. Owing to the reduction division of the chromosomes half the germ-cells would contain one of these characters and half the other.

In some cases the mixing of the dominant and recessive characters produced a blend which was different from either, but more commonly this was not the case, and an individual inheriting a dominant character from both parents (pure homozygote) could only be distinguished, by the study of his offspring, from another inheriting the dominant character from one parent and the corresponding recessive character from the other (heterozygote).

Suppose that two such characters in the Mendelian sense are the presence of the factor leading to acholuric jaundice (A) and its absence (a), then any individual may be of three possible constitutions—AA when he inherited acholuric jaundice from both parents, aa when he inherited it from neither, and Aa when he inherited it from one. If the presence of this factor is dominant to its absence then Aa will have acholuric jaundice, and will be indistinguishable from AA except by the study of his offspring; but if the presence of this factor should be recessive to its absence then Aa would not have acholuric jaundice and would appear like aa.

Most pathological conditions which are inherited are 'dominant', but albinism and alkaptonuria (20) are examples of the less common recessive type. Another uncommon type has recently been described by Brain (48) in hereditary ataxia, which depends on the combination of a rare dominant and a common recessive character.

A dominant character can be recognized by its transmission through an unbroken series of generations, since it is impossible for it to lie dormant in the germ-cells and not appear in the individual.

A recessive character is not so easily recognized, but as it can only show itself when it appears in an individual from both sides (i. e. without the corresponding dominant character from either side) it is not likely to appear in the children of two or more marriages in the same family group, unless the

character in question is a common one in the general population. Acholuric jaundice is obviously not common, and consanguineous marriages are the most likely way of bringing out an uncommon recessive character which is usually masked. This is shown in cases of alkaptonuria and albinism.

The individual with acholuric jaundice may therefore be of constitution Aa or AA, but with such an uncommon disease it is unlikely that he had inherited it from both parents, and he will generally be Aa, i. e. his sex-cells will be of equal numbers carrying a and carrying A. Suppose he marries another individual of the same constitution, equal numbers of the children will have the constitution aa, Aa, aA, and AA, but as A is dominant three-quarters will have acholuric jaundice. Such a marriage has not been reported. More commonly he will mate with an individual whose constitution is aa, and here the children will consist of equal numbers of constitution Aa and those with aa, i. e. half will have acholuric jaundice and half will not. Where two normals marry, acholuric jaundice can never be inherited, since all the children must be of the constitution aa.

The following are the three main characteristics of a dominant Mendelian character. It is always inherited directly from parent to child. Of the children (on the average) half will have the character and half will not. The former will again behave like their parents; the latter (provided they marry a normal, which is almost certain with a rare condition) will always have normal children.

The first of these laws was clearly recognized by Huntingdon in the serious type of chorea called after his name (2), before Mendel's views had become known. The second was clearly expressed by Mendel, and it is for this and many more complicated numerical relationships that he deserves great credit, as well as for his insight into the segregation and independent transmission of different characters.

Mendelian Inheritance in Acholuric Jaundice.

When the present family was first considered, in 1921, the inheritance of the disease through two apparently healthy subjects led one of us to conclude that it could not be a Mendelian dominant character (38).

About the same time Meulengracht gave a good account of eight families, including 33 subjects with acholuric jaundice, and concluded that it was always transmitted from one diseased individual to another, and that healthy individuals always had healthy children (37). In all the families with one parent affected there were 19 children with the disease and 13 who were healthy, or, if a few doubtful cases were included as what was most probable, 26 and 24. Considering the paucity of the data this proportion agrees surprisingly well with Mendel's rule, half healthy and half diseased.

It was this which led us to reopen the question, and Mr. K. was examined with the idea of proving that the disease could be transmitted through a healthy subject. The unexpected result naturally convinced us, and when Mrs. P. was also found to have typical blood changes all the cases fell into line, for all fourteen abnormal members of the family inherited the disease through parents who had the blood changes of acholuric jaundice.

In families where one parent was affected there were 38 children apart from 4 who died in infancy; of these, 14 had and 24 had not acholuric jaundice. Here, as elsewhere, the number affected is less than would be expected, but it is very likely that several latent cases may pass unnoticed. Another reason is that nearly all the younger children appear free, but some of these whose blood has not been examined may as they grow up develop acholuric jaundice. In the families of those who were free from the disease there were 26 children, and, as would be expected, all these were free.

It is important to see how far the cases which have been reported in the literature support this view. In addition to this family and another described in Appendix II, the following authors all provide evidence of its truth, namely, Wilson (3), Minkowski (4), Barlow and Shaw (6), Hutchison and Panton (17), Box (26), Elliott (32), Poynton (21), Hawkins and Dudgeon (16), Parkes Weber (22), Roth (23), Kahn (25), Gänsslen (39), and, most fully of all, Meulengracht (44).

In some of these only affected members were given, and in most the descendants of the unaffected were not given, but all agree with the two rules, that inheritance is only through the affected and the corollary that once free always free is true of any branch of the family. The important proviso here is that the freedom must be proved by blood examination and not merely by absence of signs.

Numerically the agreement is not so close, probably for the reasons already given—there being 99 affected and 127 unaffected children in the families where one parent had acholuric jaundice. From healthy parents there were 96 healthy children and none who had the disease.

Wilson noted that the disease was transmitted through an affected parent (3), and his family tree has been given in the preceding paper. In Minkowski's family (4), his patient had two children, a mother, an uncle, an aunt, and a brother, all of whom were affected; and this brother had four children, only one of whom was affected (the maternal grandparent who presumably transmitted the disease to three of his children is not mentioned). But in most of the families reported there have not been sufficient members—affected or unaffected—to provide much evidence of its inheritance until all are taken together.

In several of the families described by Gilbert and his pupils (5) there are exceptions to this, but the cases they described were jaundice of various sorts. When the cases were typical acholuric jaundice the inheritance was of this type; for example, in one family there were a father and four children affected, and in another two brothers and a sister, their father and grandfather, and perhaps their great grandfather.

The main difficulty is that in many of these families the first subject with the disease has two normal parents. Generally of course their blood has not been examined, but one would hesitate to assume such an unlikely coincidence as that all these were the rather rare type of latent case.

In one of Meulengracht's families (*loc. cit.*, No. 6, p. 102) the blood of both parents was found to be normal, so that this patient must have 'acquired' the disease *de novo* and transmitted it to one of his children. This is not assuming

that 'acquired' characters are transmitted, for the words are being used differently. With 'acquired' acholuric jaundice in the usual sense the disease is not transmitted.

Meulengracht follows Johansson's view of mutations arising spontaneously in the germ-cells and therefore capable of inheritance. De Vries has brought forward a good deal of evidence for such an occurrence and considers mutations important from the point of view of evolution (8). But there is no reason why all mutations should be useful biologically, and acholuric jaundice is one that is not. The frequent occurrence of the same mutation is a generally recognized phenomenon.

If this explanation be accepted for the first case in each family there are few records in the literature which suggest any exception to the above rules. In Family 5 of Meulengracht (*loc. cit.*, p. 102), a brother of one patient was reported to be yellow, and if so these two would have inherited it from two apparently healthy parents; as neither the brother nor the two parents could be specially examined, this can hardly be set against all his other cases (excluding the first in each family) who inherited their condition from a mother or father with the disease.

Mendelian Inheritance in some other Diseases.

Many pathological conditions which behave as Mendelian dominants have been given by Bateson (18) and Gossage (13), and acholuric jaundice can now be added to these. In some other familial diseases where the authors have not discussed the inheritance from the Mendelian point of view, the rules described almost hold good.

The following examples have merely been chosen because records of large families have recently come under our notice: hereditary angio-neurotic oedema (Ensor (7)), Milroy's disease (French (15)), fragilitas ossium and blue sclerotics (Stobie (47)), and polycystic disease of the kidneys (Cairns (49)). Some details of these are given in Table III.

TABLE III. *Proportion of Children Healthy and Affected in Families with (1) one Parent, (2) neither Parent, Affected.*

Disease.	From Healthy Parents there were		From Parents one of whom was Affected there were	
	Healthy Children.	Affected Children.	Healthy Children.	Affected Children.
Angio-neurotic oedema (7)	43	3	48	45
Milroy's disease (15)	11	1	19	11
Fragilitas ossium and blue sclerotics (47)	25	0	19	16
Polycystic kidney (49)	24	0	26	9
Acholuric jaundice	73	0	37	33
(1) this family	26	0	24	14
(2) Meulengracht (44)	47	0	13	19

Occasionally affected children have come from apparently healthy parents, which should not occur if the characters are Mendelian dominants. But these

parents may really be partial cases such as we have described, and not true latent ones in the sense used in discussing inheritance. Or the difficulty may arise from the disease developing later in life and so being missed.

This helps to explain why the groups of healthy and affected children in 'affected' families are not equal—both causes tending to increase the apparently healthy. The second difficulty is specially well exemplified in Cairns's family, where only nine children are affected and twenty-six healthy; but the character probably is a true Mendelian 'dominant' because there are in his family no affected children from healthy parents, and in the families where the members were old enough to know if the disease really was present or not the proportions were more nearly equal.

Mr. J. B. S. Haldane has drawn our attention to an interesting biological parallel with these latent cases of acholuric jaundice. Hoge (33), studying a chance mutation in *Drosophila*, which involved a tendency to reduplication of legs, found that only a small percentage showed the abnormality, whatever attempts at selective breeding were made. But if cold was applied throughout larval life half showed the abnormality and half did not, as demanded by the theory. Under normal conditions microscopic traces of the abnormality were present, traces which only became visible under the appropriate stimulus of cold. These two degrees of abnormality would correspond to the changes in the fragility of the red blood corpuscles and to the fully developed disease with increased haemolysis—the former being inherited and the latter developed in response to an external stimulus.

Morgan (34) described a similar state of affairs in the inheritance of another mutation in *Drosophila*. This consisted of pigment bands on the abdomen, which remained latent in the individual if the food was dry, but were transmitted and remained capable of subsequent development if there was abundance of water in the food supply during the larval stage. The development of hydroa vacciniforme under the influence of sunlight in inherited porphyrinuria (Garrod (20)) may be taken as another parallel.

Before discussing the effect which these latent cases have on our views of the pathology of acholuric jaundice, one or two points in the blood picture will be referred to briefly.

Some Changes in the Red Cells in Acholuric Jaundice.³

In his original paper Chauffard gave some curves showing the proportion of red cells haemolysed by various strengths of saline in different cases (12). Using a method which has been described elsewhere (50), this has been determined in most of our patients, and the results are given fully in Table IV and in

³ We should like to take this opportunity of drawing attention to a mistake in a paper by one of us (J. M. H. C.) in the last volume of this Journal (pp. 411, 412), where it was stated that in one case of acholuric jaundice the resistance of the red cells against haemolysis by saponin was found to be less than normal. This has not been the case in five patients examined since, and we think that there must have been some error in the first observation.

Fig. 1. The three thick lines give the average number of corpuscles haemolysed by different strengths of sodium chloride in acholuric jaundice before and after splenectomy, and in four normal subjects. The thin lines show the range of variability in health and in acholuric jaundice. The curve showing the average result after splenectomy is just outside the range of the disease; its range overlaps this, but not the normal area. The variability of different corpuscles in the same individual is much greater in acholuric jaundice than in health. From these curves the actual proportions undergoing haemolysis between any two points can be calculated, and these, with some corresponding figures of Meulengracht's for unwashed corpuscles (*loc. cit.*, pp. 36, 46), are given in Table V. If these are plotted on a curve the healthy corpuscles show the

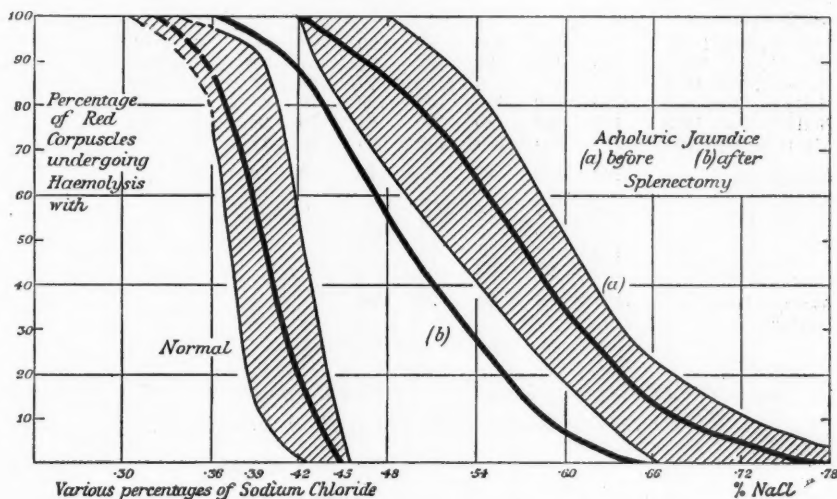


FIG. 1. For explanation see text.

normal distribution curve (as they do when their size is considered), but the corpuscles from patients with acholuric jaundice show a much flattened curve.

Complete blood counts have not been done in all cases, as many of our examinations have been made in the patient's home. In thirty counts on eight patients the most striking feature is the relatively high colour index. Only in exceptional circumstances is it below 0.75, and of eight counts where the haemoglobin percentage was below 50 the colour index averaged 0.82.

For an equally severe degree of anaemia one of us (46) found the colour index averaged 1.15 in pernicious anaemia and 0.53 in chlorosis and secondary anaemia in one hundred cases of each (see Table VI); so that while the colour index is lower than in pernicious anaemia, it is higher than in any other form of anaemia.

TABLE IV. *Percentage of Red Corpuscles undergoing Haemolysis at various Strengths of NaCl.*

Subject.	Percentage of NaCl.										
	0.00	0.36	0.39	0.42	0.45	0.48	0.54	0.60	0.66	0.72	0.78
Acholic jaundice (before operation)											
Nelly K., Jan. 11, 1924	100	100	100	100	100	90	50	40	17		
Nelly K., Jan. 24, 1924	100	100	100	100	80	67	63	52	15	1	0
Ethel P., Sept. 1925	100	100	100	100	100	100	63	34	12	9	5
Walter P., Sept. 1925	100	100	100	100	100	91	61	37	21	12	(tr)
Mrs. P., July 1925	100	100	100	100	75	67	43	34	16	6	(tr)
Mr. K., July 1925	100	100	100	100	100	98	83	51	0		
Average (6)	100	100	100	100	92	85	60	40	14	5	1
Acholic jaundice (after operation)											
Elsie P., Feb. 1924	100	100	100	80	50	27	6	0	0		
Elsie P., July 1925	100	100	91	91	91	57	30	6	(tr)		
Nelly K., Feb. 1924	100	100	100	100	97	90	62	22	(tr)		
Nelly K., Mar. 1924	100	100	100	100	100	70	38	8	0		
Nelly K., July 1925	100	100	80	80	61	50	24	6	(tr)		
Albert K., July 1925	100	100	100	100	66	36	11	3	0		
Average (6)	100	100	95	92	78	55	30	8	(tr)		
Normals (1)	100	77	14	(tr)							
" (2)	100	77	56	13	(tr)						
" (3)	100	92	76	14							
" (4)	100	97	93	55							
Average (washed corpuscles)	100	86	60	20	(tr)						

TABLE V. *Percentage Distribution of Red Corpuscles according to the Strength of Saline needed to produce Haemolysis.*

Origin of Red Cells.	Percentage of NaCl.																
	Between																
	0.30	0.33	0.36	0.39	0.42	0.45	0.48	0.51	0.54	0.57	0.60	0.63	0.66	0.69	0.72	0.75	
	0.33	0.36	0.39	0.42	0.45	0.48	0.51	0.54	0.57	0.60	0.63	0.66	0.69	0.72	0.75	0.78	
Normal * (unwashed)	2	16	42	30	10												
Normal † (washed)		14	28	38	19	1											
Acholic jaundice * (not washed)		4	9	14	23	20	12	6	3	3	2	2	1	1			
Acholic jaundice † (washed)					6	8	10	12	14	14	12	9	5	4	3	2	
Acholic jaundice † (washed after splenectomy)			4	8	15	18	15	13	11	8	5	3					

* According to Meulengracht (44).

† From this series.

TABLE VI. *Average Colour Index in Different Types of Anaemia.*

Haemoglobin percentage	20	40	60	80
Pernicious anaemia	1.10	1.15	1.20	1.20
Acholic jaundice	—	0.82	0.85	0.91
Splenic anaemia	0.65	0.70	0.75	0.85
Secondary anaemia and chlorosis	0.40	0.53	0.67	0.80

This high colour index has been commented on by others, notably by Meulengracht (*loc. cit.*, p. 8) who found in twenty-four cases it varied between 0.8 and 1.2, averaging only just under unity. Biffis has recorded three cases in which with haemoglobin percentages of 15, 25, and 25 the colour indices were 0.75, 0.88, and 1.02 respectively (31).

Under ordinary conditions this high colour index corresponds with a larger size of the red cells (45), but in the familial type of acholuric jaundice the cells

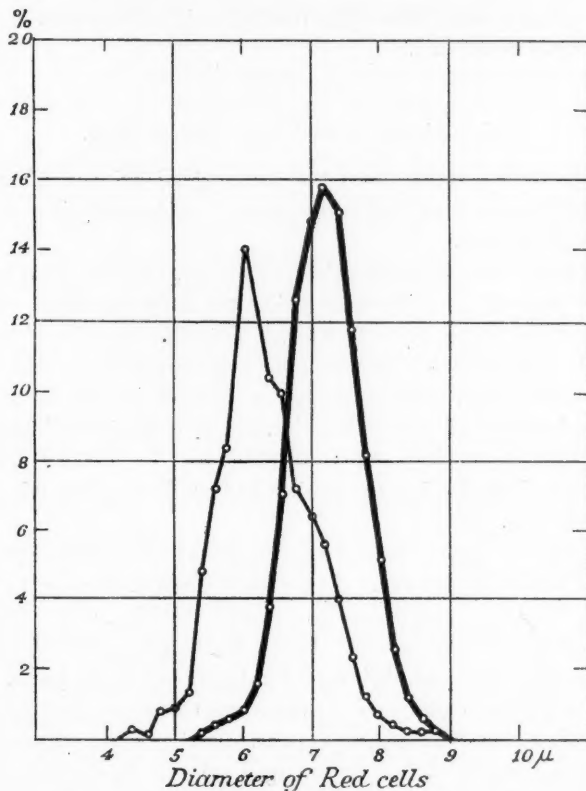


FIG. 2. Distribution curve of the red cells according to size in a healthy subject and in one with acholuric jaundice. The curve on the right represents the normal with a mean diameter of the red cells of 7.23μ . The curve on the left represents a subject with acholuric jaundice with a mean diameter of the red cells of 6.19μ . (These curves are drawn from figures supplied by Mr. A. C. Hampson and Mr. J. W. Shackle.)

are found to be small (12). This might possibly be because the haemoglobin is in a form more concentrated than usual, or probably because the volume of each red cell is increased while its diameter is diminished, i.e. it is more spherical than usual.

This is what Mr. A. C. Hampson has observed, and he has been able to diagnose acholuric jaundice on the appearance of the wet film, the cells being

spherical with a slight constriction almost like a dumb-bell. Mr. Hampson and Mr. Shackle have kindly allowed us to include a distribution curve by the Price-Jones method (36a) of the size of the red cells in a case of acholuric jaundice (Fig. 2). The small size of these cells did not correspond to a small volume, as shown by haematocrit determinations.

According to Whitcher the red cells become larger after splenectomy, and a year later are of normal size (51). If this is so, the small size must be a result of the anaemia and not an essential inherited part of the disease. It makes the contrast between the small cells of the familial and the large cells of the acquired type all the more interesting.

Discussion of Latent and Partial Cases.

These are of importance from the pathological point of view, for if the abnormal fragility may occur without other signs of haemolysis it cannot be the only cause of the disease.

Various cases have been described where some of the signs or symptoms were present without the disease assuming the fully developed form—one in which the jaundice did not appear for a long time after the other signs (Benjamin and Sluka (11)), and another in which the large spleen was noticed before the jaundice (Schlecht (28)). In one family the grandmother and father had all the typical signs, including abnormal fragility, and three of the children everything except the jaundice (Gotzky and Isaac (29)), and in another the child had typical acholuric jaundice but the mother and uncle only anaemia and splenomegaly (Ward (30)).

In the first three generations of a family described by Biffis (36) nine or ten members had acholuric jaundice. In the three where a blood examination was complete, all the usual signs, including increased fragility, were found, although the anaemia was not very severe. In the fourth generation five members of three families were examined, their ages varying from 7 to 15 years. Two were apparently normal, but three showed some signs, but not typical acholuric jaundice, i. e. two had some anaemia, one of these having also an excess of urobilin in the urine, and the third had an enlarged spleen. In the two whose blood could not be examined the fragility was increased, and possibly some of these children would later show the fully developed disease.

Elliott described a family of seven brothers and sisters, six of whom were sallow and had attacks of biliousness associated with jaundice. Though they were not anaemic, the spleen was palpable in two and the fragility increased in three, but unluckily he does not say how many were examined from this point of view (32).

Harry K. and perhaps Mrs. P. may be regarded as analogous to these patients, and it is possible that in Harry the disease may later become fully developed. According to Tileston (43), cases appearing after 30 are always acquired, but often in the familial form no signs or symptoms are noted till childhood or later.

Such patients may always have had the abnormal fragility of their red cells, while some further illness has been the actual stimulus for acquiring the fully developed disease. We are not aware of any examination of the blood of a patient who has later developed the familial or acquired type of the disease, but in the former, at any rate, it is likely that the abnormal fragility was always present.

There is another partial form of the disease more difficult to understand, where the fragility of the red cells is normal, but the other signs and symptoms are present. Widal (27) has described several 'acquired' cases in which the fragility is normal if the corpuscles are not washed with saline, but is abnormal after they have been removed from their own plasma. He has once recorded typical signs of the disease with the fragility of the red cells normal whether they were washed or unwashed. Claus and Kalberlah (9), Cade (14), and Lommel (24) have described similar cases.

In Cade's family the grandfather probably had acholuric jaundice, and the father became yellow at 25 and always remained so. Although he had served in the army in the East and had malaria and some disorder of his liver, the yellow colour was due to acholuric jaundice, for he had a large spleen, much bile-pigment in his plasma, and plenty of urobilin in his urine. He transmitted the disease to three of his seven children, who showed typical blood changes. In spite of this, the father's blood showed no changes characteristic of acholuric jaundice, the fragility was normal, the red cells were not small, and he did not have the 'hematies granuleuses' described by Chauffard.

These unusual cases are not difficult to explain from the pathological point of view, because the underlying process at work in pernicious anaemia is extremely similar to that in acholuric jaundice; indeed in some of the acquired cases it is difficult to decide on the diagnosis, and border-line cases have been described (19, 27). As regards hereditary cases it is difficult, because presumably the increased fragility is the essential basis which allows the development of a haemolytic anaemia. So far the atypical cases reported are too few to upset this view, for which there is a good deal of evidence.

Absolutely latent cases like Mr. K. seem to have been observed, rarely, if at all. Meulengracht examined the resistance of the red cells eight times in brothers or sisters of inherited cases, and eight times in the other members of their families. In all he found the resistance normal. In this family of ours nine other patients have been examined with the same result.

Giffin (35) found that a patient's mother, who had never had any suggestive signs or symptoms, showed complete haemolysis of her red cells with 0.40 per cent. NaCl. He did not record the point at which haemolysis commenced, but in the normals it was complete at from 0.32 to 0.39 per cent. NaCl, and in the cases of acholuric jaundice at from 0.40 to 0.47, so that the abnormal fragility is not very convincing.

These incomplete forms of acholuric jaundice, especially Mr. K. and Mrs. P., show that red corpuscles with low resistance to haemolysis by saline do not always produce obvious signs or symptoms of acholuric jaundice. In both

patients examination revealed some increased haemolysis which was not sufficient to give rise to the usual yellow colour. In one the spleen was considerably enlarged, but in the other it was not. In both, and in Harry K., there was freedom from all symptoms although the fragility of the red cells was greatly increased.

This can readily be understood if the increased fragility is the underlying basis on which the disease may develop, and if infection or some other cause then starts the spleen on its career of excessive haemolysis—a view to which we were led by considering the relatively small improvement in the resistance of the red cells after splenectomy, compared to the great improvement of all other signs and symptoms (50).

Apart from a few anomalous cases where the fragility was normal, most of these other partial forms of the disease agree in the yellow colour and signs of haemolysis being absent. To some extent this is only an exaggeration of what is found intermittently in many cases of acholuric jaundice, and Mrs. P. and Harry K. really belong to this group, but in Mr. K. the process has gone farther, because nothing at all appeared abnormal until blood examination showed well-marked fragility and slight haemolysis.

Conclusions.

The abnormal fragility of the red cells may occur without the other signs and symptoms of acholuric jaundice, both in ordinary cases after splenectomy and in latent cases. When due allowance is made for these, acholuric jaundice is inherited as a 'dominant' Mendelian character.

We wish to thank Dr. Fawcett and Dr. Ryle, under whose care some of this family were respectively in-patients and out-patients at Guy's Hospital, and Dr. Hutchison, under whose care others were in the London Hospital.

APPENDIX I. HISTORY OF A FAMILY WITH FIFTEEN MEMBERS WITH ACHOLURIC JAUNDICE IN FIVE GENERATIONS.

I. First Generation.

1 is said to have had jaundice for many years of her life. Her granddaughter, Mrs. P., remembers that she was once housekeeper to Sir Frederick Taylor, who was much interested in her condition, but we have not been able to find any reference to her in his Lumleian lectures on 'Diseases of the Spleen' or elsewhere. She had only one daughter and lived to an old age. Nothing is known about her husband.

II. Second Generation.

1 (born c. 1845) is said to have been yellow for many years before she died. Her daughter, Mrs. P., and her son's (Mr. K.'s) wife, who had not seen each other for many years, gave a very similar account of her appearance and of the early

family history, in most particulars of which they were corroborated by the report referred to below. It is not known at what age she became yellow, but in 1897, when her daughter (Mrs. E.) was in the London Hospital, she and her husband were both described in the report as 'healthy'. She lived to be nearly 70, and had first three children, then some miscarriages and children who died in infancy, and then two more children.

III. Third generation.

1, Mrs. P. (b. 1865), has been fully described in the text. Without having had any symptoms of the disease, her red cells showed increased fragility, her spleen was greatly enlarged, and there was evidence of abnormal haemolysis. She had twelve children and two miscarriages.

2, Mr. K. (b. 1868), has also been described in the text. He had lived a strenuous life without any symptoms of the disease, but his red cells showed increased fragility and there was evidence of abnormal haemolysis.

3, Mrs. E. (b. 1870), was admitted to the London Hospital in 1897, complaining of pain in the left side, swelling of the legs, weakness, and shortness of breath of eighteen months' duration. She had become worse after the birth of a child which died three weeks later in convulsions, and about this time herself noticed a swelling in the left side of the abdomen. Though she gave no history of chorea or rheumatic fever Mrs. E. had a mitral presystolic murmur, so that no doubt the condition of her heart accounted for some of her symptoms. Her spleen filled the left side of the abdomen and descended eleven inches below the 7th rib. She had been a dark sallow colour for some years and was very anaemic—haemoglobin 35 per cent., red cells 2,000,000, and white cells 70,000 per c.mm. The diagnosis made was leucocythaemia. She lived for another six years after leaving hospital, during which time she had one child who died young, and another who was and still is healthy. In view of this long history, the large spleen, the sallow colour, and the anaemia, it seems probable that this was really acholuric jaundice occurring before the disease was recognized.

4 (b. 1880) has always had good health. He was a soldier before and during the war and appears of unusually good physique. His blood was examined and showed normal fragility.

5 (b. 1882) was reported to be quite healthy.

IV. Fourth generation.

1-12 are the children of Mrs. P. and her husband, who is still alive and appears in good health. In 1921 (38) the available information about this branch of the family was very scanty and rather inaccurate.

1 (b. 1887) died, probably from diphtheria, when about two years old after being yellow for some time. The mother then lost her milk, and 2, who was a few months old, died with convulsions.

3, Walter P. (b. 1890), was quite well till he was nine years old, when he was admitted to the London Hospital with four days' history of acute nephritis—vomiting, pains, and swelling under the eyes. The urine contained albumin. He had had scarlet fever two years before. He complained of pain in the left side, but the spleen could not be felt. He made an uneventful recovery and was discharged to a convalescent home. These facts have been taken from the old report, but the following are from his own account.

While at the convalescent home he became 'very jaundiced', but does not know how long it lasted (he was only nine years old). Since then he has been yellow from time to time, the worst attack being in 1924, when he was 34. Generally the yellow colour is not deep and he merely notices it in the glass and tells his wife 'that it is one of his off days'. He feels languid and unable to do anything and the attack generally lasts two or three days. These attacks have been fairly frequent and have been getting more so.

When examined (Sept. 1925) the conjunctivae just showed a trace of yellow, but his skin would have been passed as normal. The plasma contained a little bile-pigment and the urine contained some urobilin and a larger amount of urobilinogen. The spleen was enlarged two inches below the costal margin. The red cells showed abnormal fragility (see Table I). The haemoglobin was 84 per cent., the red cells 4,360,000, and white cells 16,800 per c.mm.; he looked fit and practically never had to miss his work as a compositor. In appearance he was not an obvious case of acholuric jaundice, but the diagnosis could have been made on the history and an ordinary clinical examination, apart from the increased fragility of the red cells.

4 (b. 1891) was yellow at birth and remained a yellowish-green colour until his death a year later. The doctor who made a post-mortem examination said 'the spleen was large enough for a man of sixteen stone'.

5 was quite free from any symptoms of the family disease, but died when 18 years old from heart disease. She was said to have had mitral stenosis.

6, Elsie P. (b. 1895) had a severe form of acholuric jaundice which started with an acute illness simulating typhoid in 1909. She was then admitted to the London Hospital, with headaches, vomiting, shivering, and abdominal pains. Her spleen was enlarged three inches below the costal margin. She was anaemic and yellow in colour. For seven days her temperature was 100–101°, and probably because of the severity of her cholaemia the plantar reflexes were reported to be extensor. She had been of an unusual colour for some years, with exacerbations in which she became definitely yellow. Two years later she was readmitted. Her anaemia was less, but her spleen was now palpable below the umbilicus. A haemic bruit was present, and there was oedema of the legs. Twice during her stay in hospital she developed moderately severe attacks of purpura. Bile-pigment was present in her serum, but not in the urine, and the fragility of her red blood corpuscles was increased, partial haemolysis occurring with 0.6 per cent. NaCl (see Tables I and IV). Three years later, in 1914, she was again admitted. Her physical condition was similar, and previous findings were again confirmed.

In 1909 her haemoglobin was only 15 per cent.; in 1911, 65 per cent.; and in 1914, 35 per cent. There was moderate poikilo- and aniso-cytosis, and when her anaemia was most severe megaloblasts and nucleated red cells were found. She was under the care of Dr. Robert Hutchison, to whom I am indebted for permission to include these investigations.

When seen seven years later, she appeared a young woman of average health, and was pale but not yellow. Since 1914 she had been able to do ordinary household work, but had often been under treatment for anaemia, and often became yellow. In 1923 she had periodical attacks, when her colour became deeper, and as she was frequently incapacitated from her ordinary household work she was admitted into hospital, and Mr. Rowlands removed her spleen in November of that year; it weighed 980 grm., and sections showed that there was some fibrosis of the pulp with atrophy of its cells, dilatation of the capillaries, and atrophy of the Malpighian corpuscles. She made a good recovery from the operation and in 1925 was in good health except for 'indigestion'. She was not anaemic and had quite lost her yellow colour, but the fragility of her red cells, which had improved a little six months after the operation, had returned nearly to its previous condition (50).

7 (b. 1898) looked a little anaemic and her complexion suggested that she might be a very mild case of acholuric jaundice. Her spleen was not palpable, and unfortunately the blood which was brought away for examination was spoilt. There has been no opportunity for a second examination, so, in the absence of any definite evidence to the contrary, she and her daughter have been included as normal.

8 (b. 1900) complained of nothing but dysmenorrhoea. She was of normal

complexion, not anaemic, and the spleen was not palpable. Physically she did not greatly resemble any of the patients with acholuric jaundice.

9 (b. 1902) and his son were not seen, but were said to be healthy.

10, Ethel P. (b. 1904), was treated at the Evelina Hospital for anaemia before she was a year old, and the spleen was then palpable but not much enlarged. When five years old she was still anaemic and had a large spleen. She continued to have attacks of anaemia and jaundice, but does not seem to have been greatly inconvenienced by them and was able to work in a chocolate factory. When examined (September 1925) she was a typical case of acholuric jaundice. The skin and conjunctivae were yellow and the plasma contained bile-pigment. She was anaemic (haemoglobin 60 per cent., red cells 2,900,000, and white cells 10,800 per c.mm.), and the spleen was palpable three inches below the costal margin.

11 (b. 1906) was always clay-coloured and suffered from anaemia. At fifteen months old he was in the London Hospital under the care of Dr. Robert Hutchison, when his spleen was much enlarged and his haemoglobin 45 per cent. He was discharged, but died suddenly some time later.

12 (b. 1908) showed no signs of the disease in 1925, and in appearance was quite unlike any of those with it.

13-24 are the children of Mr. K. and his wife, who had always had good health.

13 (b. 1890) appeared healthy and her spleen was not palpable; of her six children one died of pneumonia, two were examined clinically but not haematologically, and appeared normal, and the others were said to be so.

14 (b. 1892) had good health until he was 20, or at any rate he was free from attacks of jaundice. He was then admitted to the Seamen's Hospital at Greenwich, and after a long illness, complicated with empyema and jaundice, he died. *Post mortem*, stenosis of the mitral valve was found, and there were calcareous nodules in the cusps. The liver was much enlarged and showed multilobular cirrhosis. The spleen was not mentioned, so was probably normal. In the absence of splenomegaly and a long history of jaundice, it seems unlikely that he suffered from the family disease. His mother distinguished quite clearly in her own mind between the jaundice from which he had suffered and the jaundice of two of her other children.

15 (b. 1894) always had good health till serving at Salonika during the war, when he frequently suffered from malaria. After the war he served in India, and in 1922 was in hospital there dangerously ill with jaundice and a large spleen, when a diagnosis of malaria was made. It seemed most probable that he had acholuric jaundice, but when examined in July 1925 his spleen was no longer palpable, his colour was the brownish tint of malarial and other anaemias, and there was nothing in the colour or history to suggest acholuric jaundice.

The subsequent discovery that his father's red cells were abnormally fragile, although he had no signs of the disease, led us to examine him again more thoroughly. He was rather anaemic, but the red cells showed normal fragility, his plasma did not contain bile-pigment, and his urine showed no excess of urobilin. His only son was said to be normal.

16, Nelly K. (b. 1896) was noticed to be yellow as a baby, and throughout childhood she had 'bilious attacks' with vomiting, when her colour became deeper. When 20 years old she was admitted to Guy's Hospital under Sir William Hale-White for pain in the left side and vomiting. She was in hospital three times during the year without much change. Her colour was always yellow and became deeper on occasion, when she had attacks of vomiting and pyrexia. During one of these attacks her urine contained bile-pigment and urobilin, but there was not a complete obstructive jaundice. Her spleen was much enlarged—at least six inches below the costal margin—but her liver was not felt to be enlarged. Several blood counts were done with very similar results—

haemoglobin 78 per cent., red cells 4,500,000, white cells 13,000 per c.mm.; Apart from the jaundice, the anaemia, and the very large spleen, her physical condition seemed normal. She was married soon after her discharge. Two years later she was readmitted for uterine haemorrhage, and a two months' abortion followed. Her anaemia was more severe—haemoglobin 56 per cent.

In 1920 she was admitted under Dr. Fawcett. Her general condition was fair, but she complained of pain in the side and fainting attacks. She was four months pregnant. Her skin and conjunctivae were yellow, and she looked anaemic. The spleen was much enlarged—apparently the same size as in 1916. Her blood count showed a more severe anaemia than previously—haemoglobin 38 per cent., red cells 1,800,000, white cells 10,000 per c.mm. Some anisocytosis, slight poikilocytosis, and a few nucleated red cells were observed. Her urine contained no bile-pigment, but a large amount of urobilin, and her blood-serum contained urobilin and bile-pigment. The fragility of her red cells was much increased (see Tables I and IV).

She was treated with iron and arsenic as an out-patient, and five months later, before her confinement, her haemoglobin had risen to 62 per cent. The fragility of the red cells was not much changed. The yellow colour was less noticeable than any time she could remember. The enlargement of the uterus had pushed the spleen upwards and to the left. This caused a good deal of pain and was the only symptom of which she complained. Her labour was uneventful, and the child appeared healthy.

Largely because of the much greater discomfort and disability of her second pregnancy, and because in October 1923 she appeared in such bad condition compared with her brother, she decided that it was worth while having an operation. In January 1924 Mr. R. P. Rowlands removed the spleen and also the gall-bladder, as the latter contained a large number of small pigment stones; during one of her attacks of vomiting and pyrexia her urine had contained bile-pigment, but her faeces then appeared to contain the usual amount of pigment, and she had never had any symptoms pointing to gall-stone colic.

Examined two years after her operation she was in excellent health and the haemoglobin percentage was 92. There was no bile-pigment in the plasma, but still a slight excess of urobilin in the urine (50).

17 (b. 1899) and her three children are said to be quite healthy.

18 (b. 1900) shows no jaundice, anaemia, or splenic enlargement; nor does her son, who has spastic diplegia.

19, Harry K. (b. 1903), has been described in the text. Abnormal fragility and a palpable spleen were the only signs of the family disease.

21, Albert K. (b. 1908), was jaundiced at birth, and though this cleared up after a month, he had always been slightly yellow, and liable to attacks of shivering and vomiting, when he became a deeper yellow. He was admitted under Dr. Fawcett after one of these attacks. His spleen was palpable about four inches below the costal margin, but the liver was not felt to be enlarged. His heart was slightly enlarged and there was a systolic bruit. His plasma contained urobilin and bile-pigment. His blood count was—haemoglobin 69 per cent., red cells 4,800,000 per c.mm. His red cells showed abnormal fragility (see Table I).

He improved for a time and attended as an out-patient, but little or no progress was made. He had always been small for his age and did not appear to be growing. His health was far from satisfactory, and it seemed that unless something more could be done to help him he would be unable to earn his living, especially as his haemoglobin was often as low as 50 per cent.

His spleen was removed by Sir Alfred Fripp in November 1921. After the operation there was a rapid change in the fragility of his red cells, and the haemoglobin percentage rose to 78, but even at the beginning of 1923 the improvement in his general condition was not what had been expected. However,

by October, two years after the operation, he had grown considerably and had improved very much. Examined four years after his operation he was in excellent health and the haemoglobin percentage was 95. There was no bile-pigment in the plasma, though there was still a slight excess of urobilin in the urine (50).

22 (b. 1909) died of diarrhoea in infancy.

20, 23, and 24 (b. 1905, 1911, and 1913) showed no evidence of anaemia, jaundice, or splenic enlargement in 1921.

25-29 are the children of III. 3, who died of what was probably acholuric jaundice.

25 (b. 1893) is said to have had good health, but was killed in France during the war; he left one son who is healthy.

26 (b. 1895) was in good health, but was not examined. His only child was also said to be healthy.

27 and 28 died in infancy.

29 (b. 1900) had always had good health, and when examined in September 1925 showed no signs of jaundice, anaemia, or splenic enlargement. The fragility of her red cells was normal. Her son appeared quite healthy, but his blood was not examined.

30-38 (born at fairly regular intervals from 1905 to 1921) are the children of III. 4 and his wife, both of whom are healthy. All are reported to be free from the family disease, and no evidence of it could be found when they were examined in 1921, but the blood was only examined in 30, in whom it was found normal. 32 suffered from bilious attacks, 33 from chorea, 34 from rheumatism, and 38 was in Guy's Hospital with cyclical vomiting; 36 died of measles as a small child.

39 (b. 1910) was the only child of III. 5. In 1921 his blood was examined and found normal, and he showed no evidence of the family disease.

V. Fifth generation.

1 and 2 (b. 1911 and 1913) are children of Walter P. (IV. 3), and the elder is so far the only subject where the disease has appeared in the fifth generation. Always yellow and said to have had some trouble with his spleen, he died when five months old. The younger is reported to be quite well and free from any symptoms.

3 and 4 (b. 1917 and 1919), the children of Elsie P. (IV. 6), have both been examined without our finding any definite signs of the disease. The elder was rather anaemic, but his red corpuscles showed normal fragility.

14, 15, and 16 (b. 1921, 1923, and 1925) are the children of Nelly K. (IV. 16). All three so far appear free from any signs of the disease. The blood of the eldest, taken from the umbilical cord at birth, showed normal fragility, so that evidently the placenta acted as an efficient barrier against the transfer of the agent responsible for the increased fragility.

The other three affected members of the fourth generation are not yet married.

In the fifth generation the sixteen children (5-13, and 17-23) of healthy parents are all said to be free from any signs of the family disease. Only four have been seen (7, 9, 20, and 23), and no evidence of jaundice, anaemia, or splenic enlargement could be found, but the blood was not examined and most of them are not yet five years old.

APPENDIX II. HISTORY OF A SECOND FAMILY IN WHICH THERE WERE FIVE MEMBERS IN FOUR GENERATIONS WITH ACHOLURIC JAUNDICE.

I. First generation.

1 is said to have had jaundice for years, but lived to be 70.

II. Second generation.

1 died when 36 years old after being frequently jaundiced. He had no children.

2, 3, and 4 all died when middle-aged, but had, as far as is known, no trouble with jaundice or enlarged spleens. 2 had four children who were healthy and 3 had three children who were all healthy. 4 had no children.

5 was born in 1867 in Portsmouth. She was ailing as a young married woman and was in the Westminster Hospital in 1899, six months after her third child (III. 10) was born. Her spleen was then enlarged. She has been yellow on and off for a great many years, but does not remember if it had started then. In 1912 she attended St. Thomas's Hospital and her spleen was then enormously enlarged.

In 1925, when 58 years old, she still seemed in good health, though the spleen was enlarged at least six inches below the costal margin. Her haemoglobin percentage was 64. The fragility of her red cells was increased, there being slight haemolysis at 0.66 and considerable haemolysis at 0.48 per cent. NaCl.

III. Third generation.

1-7 have been mentioned and were all said to be healthy.

8-12 were the children of II. 5, and were born at fairly regular intervals from 1891 to 1906.

8 and 11 were examined at St. Thomas's Hospital and were said to be healthy when aged 8 and 21.

9 and 12 died in childhood after whooping-cough and enteritis. As far as is known there was no jaundice or splenic enlargement.

10 was born in 1899. She was rather anaemic at birth and had pneumonia when 4 years old, and later scarlet fever and measles. When 7 years old she had deep jaundice, and after that was yellow from time to time. When 12 years old she was told that she had the same trouble as her mother, and about this time she became rather worse.

When first seen in 1924 she felt rather tired and languid, but was not seriously troubled, as she was able to carry on with her ordinary household work. The spleen was enlarged nearly two inches below the costal margin. She was a yellow colour and a little anaemic. Haemolysis of the red cells was absent with 0.66, slight with 0.60, and nearly complete with 0.42 per cent. NaCl.

A year later, after a miscarriage at three or four months, she became worse. The yellow colour was deeper and she was less able to do her work. The haemoglobin percentage was 74, and a few weeks later 82. Her colour index was above unity and the white cells were 10,600 per c.mm. The spleen was larger than before, and the liver was palpable below the costal margin, but this disappeared after two or three weeks as she improved. Curiously enough the red cells appeared a little less fragile than before, haemolysis commencing at 0.54 and being considerable at 0.48 per cent. NaCl. The plasma contained bile-pigment and the urine excess of urobilin. She improved somewhat with iron and arsenic.

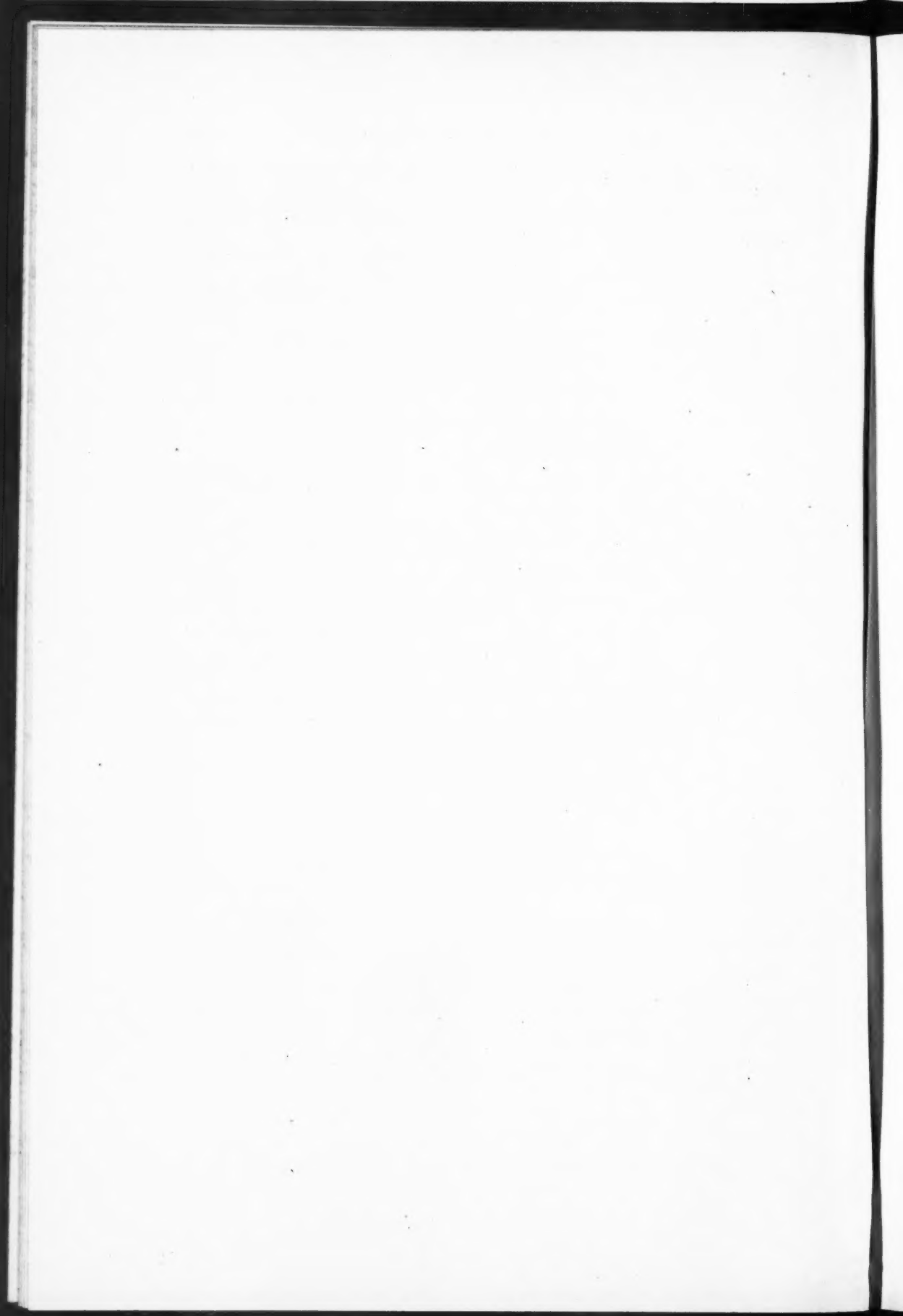
IV. Fourth generation.

1, the only son of III. 10, was born in 1921. He was said to be in good health though of small size and rather backward in development. But when examined, his spleen was palpable one inch below the costal margin, and his haemoglobin was only 50 per cent. His urine contained a slight excess of urobilin, and the fragility of his red cells was just the same as those of his mother, i.e. commencing at 0.54, and considerable at 0.48 per cent. NaCl.

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A FURTHER CONTRIBUTION TO THE STUDY OF CON- GENITAL PORPHYRINURIA (HAEMATOPORPHYRIA CONGENITA)¹

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With Plate 28

Now that the physiological action and therapeutic uses of light and actinic rays are receiving so much attention, additional interest attaches to the study of those rare individuals upon whom, because of an eccentricity of their chemical processes, these agents, usually so beneficent, inflict grave injury. During the three or four years which have elapsed since our previous paper on congenital porphyrinuria (1) was published there have been notable additions to our knowledge of the chemical nature and spectroscopic properties of the porphyrins, and of their place in animal metabolism, normal [and abnormal. It must not be assumed that, because the presence of these pigments in large amounts leads to serious damage of parts exposed to light, their influence is always harmful: for it may well be that the minute quantities of porphyrin present in normal tissues render good service. The interesting observations of van Leersum (2) upon the effects of administration of haematoporphyrin to rachitic rats point in that direction.

In the case of the boy whose case we described there have been fresh developments which call for discussion in the light of the most recent knowledge; for few anomalies raise so many side-issues as does congenital porphyrinuria, and many of its problems are still unsolved. We propose therefore, after we have reported briefly upon the present state of our patient, to explore more fully some of these by-paths.

The Present State of the Boy G. L.

The boy, who has now reached the age of $9\frac{1}{2}$ years, remains bright and intelligent, and shows no arrest of growth or development. His height and weight still conform to Galton's averages for his sex and age. It is noteworthy that, whereas an X-ray picture of his hand taken in 1921 showed conspicuous delay of ossification of the lower epiphysis of the ulna and some of the carpal bones, a similar picture taken in November 1925 shows the normal stage of ossification for his age. Not only has ossification no longer been delayed, but arrears have actually been made up.

¹ Received March 8, 1926.

The liability to develop hydroa vacciniforme upon exposed areas of skin persists, but the scarring which such eruptions produce has not increased so much as might be expected. Doubtless this is mainly due to his mother's care, and to a growing recognition on the boy's part of the expediency of avoidance of undue exposure to sunlight. His knees, which are now protected by long stockings, show no fresh lesions. There is pigmentation of exposed skin, but no undue growth of hair upon the face nor elsewhere. The vulnerability of the skin of exposed parts under slight traumata, described by Mr. Heath in his report included in our earlier paper, is if anything more pronounced, and even the trifling injury inflicted by cleaning the ear with cotton-wool moistened with spirit, in preparation for a blood count, suffices, even in winter, to produce a raw bleeding surface. It is interesting to note that Robert Liveing, in his book on skin diseases, published about fifty years ago, stated that the 'neurotic excoriations' of Erasmus Wilson are allied to bullous hydroa (3).

The skin and subcutaneous tissues of the hands are unduly firm and inelastic; and we are obviously confronted with an early stage of the lesions seen in cases of the same disorder in adults, and which may go on to permanent deformities, fixation of joints, and absorption of phalanges. Already the boy cannot straighten his fingers completely, and in the most recent X-ray picture there are seen some areas of faint shading in the soft tissues of the hand.

The appearance of the urine is unchanged, and its port-wine colour is subject only to minor variations from time to time. In this respect the case differs from most of the recorded examples of congenital porphyrinuria.

The colour of the teeth has undergone some further change, and is now rather brown-purple than brown-pink. Some of the milk teeth have been shed, and the permanent teeth which have replaced them have the same colour, but slightly less intense.

Physical examination shows nothing amiss with the thoracic organs. The most striking change is conspicuous enlargement of the spleen and liver, which causes some obvious protruberance of the abdomen. Three years ago the spleen was not palpable; now it reaches no less than three inches (7.5 cm.) below the costal margin in the left nipple-line. In January 1925 it was of about the same size as now, but in the summer appeared slightly smaller. The liver was not felt in January 1925, in July it was palpable below the ribs, and is now two inches (5 cm.) below them in the right nipple-line, and three inches (7.5 cm.) below the tip of the ensiform cartilage.

When the boy has been under observation no disturbance of temperature or pulse has been noted.

The Nature of the Abnormal Pigments in the Urine and Faeces.

It was mentioned in our earlier paper that the chemical examination of the urine and faeces of G. L. gave results in agreement with those obtained by Hans Fischer (4) in another case. (That patient, who will be referred to in future as 'Petry', was investigated in turn by Hans Günther, Hans Fischer, Schumm, and Fraenkel, from whose work most of our knowledge of congenital porphyrinuria has been derived. Petry died recently, and by the kindness of Professors Borst and Hans Fischer we have been favoured with advance copies of the protocol of the autopsy, and also of the chemical findings which have recently been published (5).) Mr. E. N. Allott, who was good enough to undertake the investigation in our case, had intended to have published his results at length, but circumstances have hitherto prevented his carrying the work farther, and he

has furnished us with the following preliminary report to be included in this paper. Mr. Allott writes:

'I received specimens of the boy's urine from time to time in gallon jars, and thymol was always added to prevent decomposition. The different specimens varied to some extent in depth of colour, from that of dark port wine to an appreciably paler reddish-brown tint. Had day to day specimens been available the variations would, almost certainly, have been more pronounced. In most samples the characteristic porphyrin spectrum was visible when the urine was examined directly with a direct-vision spectroscope. When the bands were not clearly seen in the untreated urine those of the "acid" spectrum appeared on the addition of a mineral acid.

'The faeces were sent in glass jars, without any preservative. Unlike the urine, the fresh faeces showed no abnormality of appearance. The first occasion on which the presence of abnormal pigment was observed in them was when the faecal residue, after extraction with alcohol and ether to remove lipoids, was extracted with alkali. The filtrate had a deep yellow colour which darkened on standing.

'The porphyrins were extracted from the urine and faeces in the form of methyl-esters, as described by Fischer (6). The quantities present were not estimated carefully, as each sample of urine represented the output of several days, and an investigation such as Fischer described (7) was impracticable. On the whole, I should say that, in this case, the output *per diem* was considerably greater in the urine than in the faeces.

'The melting-points of the methyl-esters of the urinary and faecal porphyrins, respectively, were 283° (with decomposition) for the urinary product, and 248° for faecal. Fischer's melting-points are 290° (with decomposition) for his uroporphyrin, and 249-50° for coproporphyrin²; the differences are doubtless due in part to differences in the rate of heating.

'The absorption spectra of the two porphyrins were measured by means of a direct-reading prism spectroscope. The results agree generally with those of Fischer, who used a prism spectroscope (8), and Schumm (9), who used a grating instrument, and carried out both direct and photographic observations. In acid solutions the bands agreed closely with Schumm's bands i, ii, and iii, which also agree closely with Fischer's readings. Schumm's bands iv and v (526.3 and 511.8 for uroporphyrin, 524.5 and 509.3 for coproporphyrin) were not seen. The readings are tabulated below:

Uroporphyrin in N/10 Alkali.

Observer.					
E.N.A.	λ 610	λ 574*	λ 560*	λ 537.5	λ 502.5
Fischer	λ 609.5	λ 571.5	λ 557	λ 536.5	λ 502.5
Schumm	λ 611.3	—	λ 559.3	λ 538.4	λ 501.8

Copro- (Sterco-) porphyrin in N/10 Alkali.

E.N.A.	λ 616.5	λ 569.5	λ 538	λ 502*
Fischer	λ 616.5	λ 569	λ 534	λ 501
Schumm	λ 617.5	λ 565.5	λ 538.3	λ 503.3

* These bands were very faint and hard to measure.

Uroporphyrin in Hydrochloric Acid.

				Strength of Acid.
E.N.A.	λ 596	λ 577.5	λ 554	25 per cent.
Fischer	λ 594	λ 573.4	λ 551	19 "
Schumm	λ 596.7	λ 577	λ 553.4	25 "

² When our earlier paper was written Fischer called the faecal pigment 'kothporphyrin'; which, on the analogy of stercobilin we rendered as stercoporphyrin. Since then, the Greek equivalent coproporphyrin has come into general use, and will in future be employed by us.

Copro- (Sterco-) porphyrin in Hydrochloric Acid.

E.N.A.	λ 592	λ 570	λ 548	20 per cent.
Fischer	λ 592	λ 570	λ 548	19 "
Schumm	λ 593.1	λ 573.5	λ 549.9	25 "

'The agreement of the above results with those of previous observers suffices to show that the principal pigments in the urine and faeces respectively were identical with the uroporphyrin and coproporphyrin of Hans Fischer. The presence of coproporphyrin in small amount in the urine of Petry was demonstrated by Fischer, but, owing to difficulty of transport of sufficient volumes of urine, this was not looked for in the present case.'

The more recent work of Fischer and of Schumm has shown that the pigment present in traces in normal urine, and in larger amounts, but still traces, in many morbid urines, including that of sufferers from lead poisoning, is coproporphyrin; and Fischer has pointed out that the spectroscopic measurements made by one of us (A. E. G.), more than thirty years ago, bear witness to that fact (10).

On the other hand, it becomes almost certain that the chief abnormal pigment in all port-wine coloured urines in cases of porphyrinuria, either acute, toxic, or congenital, is the uroporphyrin of Fischer, which differs from coproporphyrin in having four extra carboxyl groups in its molecule. By removal of these carboxyls uroporphyrin may readily be converted into coproporphyrin, but both differ from the haematoporphyrin of Nencki in the fundamental structure of their molecules. So much so that Fischer holds that they cannot be derived from the haemoglobin of the blood, and suggests the existence of a β haemoglobin, or a possible source in the pigment of muscle.

It is probable that the formation of uroporphyrin in cases of porphyrinuria facilitates the excretion of the abnormal pigment by the kidneys, but at the cost of increased sensitivity to light.

Coproporphyrin is a very widespread animal pigment, and Hans Fischer has recently found it in vegetable structures and products, such as yeast and the milk of coco-nuts, in spite of every care to exclude possible animal contaminations. Thus coproporphyrin appears at a very early stage of organic evolution, long before haematin, and Fischer (11) suggests that it may be, in man, of the nature of a vestigial remnant; a relic of a scheme of metabolism early abandoned as being disadvantageous, but which, in the rare subjects of porphyrinuria either acute or congenital, awakes to activity, much to the detriment of the individuals concerned.

The source and origin of the abnormal output of porphyrins in the anomaly under discussion is still unknown. We do not even know whether they are products of anabolism or catabolism. It would seem that the tempting hypothesis that the excreted porphyrin represents an intermediate stage in the unfinished conversion of haemoglobin into bilirubin must be abandoned, not only on grounds of chemical structure, but also because evidence is forthcoming that bilirubin and its derivative urobilin are formed in the ordinary way, and in no obviously diminished amounts, by porphyrinurias.

The Blood Picture in Congenital Porphyrinuria.

Hitherto, one of the chief difficulties in the study of the subject has been to reconcile the large and persistent output of pigments so closely akin to blood and muscle pigments, with the lack of any obvious sign of excessive haemolysis, on the one hand, or of deficient formation of haemoglobin on the other. For although in one or two cases grave anaemia has developed at a late stage, a porphyrinuric may pass continually, for years, urine of the colour of port wine, but yet may maintain a red corpuscle count and a haemoglobin percentage within the normal limits. If, as is conceivable, the metabolism of haemoglobin is in no way involved, this will present no difficulty, but recent observations have brought to light some interesting points in connexion with the blood pictures of porphyrinurics.

Blood counts are on record from several cases of congenital porphyrinuria, but counts repeated at considerable intervals are only forthcoming in the case of Petry and in that of a man originally described by Ehrmann (12), and who has, for some time past, been under observation by Robitschek (14). For this reason the following counts made by one of us (L. M.), with an interval of four years, are of special interest:

<i>Blood of G. L.</i>	<i>September 1921.</i>	<i>November 1925.</i>	<i>February 1926.</i>
Red corpuscles	4,480,000	4,540,000	4,504,000
Haemoglobin	90 %	85 %	80 %
Colour index	1.004	0.94	0.8
Leucocytes	11,600	6,800	7,600
Polymorpho-nuclears	56 %	47 %	For differential count, see p. 362.
Small lymphocytes	38 %	46 %	
Large lymphocytes	4 %	4 %	
Eosinophils	1 %	2 %	
Large hyaline	1 %	—	
Mast cells	—	1 %	

In a short preliminary note by A. M. H. Gray, published in April 1924 (13), it is mentioned that Price Jones, who had examined the blood of the patient, a girl aged 16 with congenital porphyrinuria, concluded that she was producing red corpuscles in excess, as evidenced by the presence of large numbers of immature (polychromatosis and stippled cells) and nucleated red corpuscles. Price Jones put forward the most interesting suggestion that the increased manufacture of red corpuscles was compensating for an abnormal breakdown, with the result that the number of erythrocytes was maintained at about the normal level. Not long afterwards Robitschek (14) enunciated, independently, exactly the same hypothesis, but on opposite grounds. His estimates, on seven successive days, and by two different methods, of the iron in the urine of his patient, a man of 50 years, gave a mean of 8.5 mg. *per diem*, a figure considerably above the normal. From this he concluded that an excessive haemolysis was in progress, and was balanced by an abnormal production of red corpuscles.

A priori we may well suppose that, as with so many other regulated

processes in the organism, a normal level can be maintained in spite of differences in the activity of processes; just as abnormal losses in war may be replaced by fresh drafts, and so a battalion may be kept up to strength until the supply of recruits begins to fail. But, as far as we are aware, such adaptation has not hitherto been suspected in connexion with blood-corpuscle formation and destruction; and, as it was obviously important to ascertain how far Price Jones's observations hold good for our case also, we submitted films, and the figures from other recorded cases, to Dr. A. G. Gibson, who has been good enough to examine them, and has furnished us with the following report:

'Blood slides of this case were carefully examined in January and in November 1925 and in February 1926. The first count of 500 cells is as follows:

Polymorphs	49.0 per cent.
Lymphocytes	36.8 "
Endothelial cells	13.8 "
Eosinophils	0.2 "
Mast cells	0.2 "

'The endothelial cells include certain large cells with rounded or kidney-shaped nucleus with pale or slightly bluish protoplasm (Leishman's stain) and occasional sparse reddish granules. Punctate basophilia and polychromatomasia were marked. Two nucleated red cells (normoblasts) were seen in a careful survey of the slide after the count had been made. Platelets were present in moderate numbers.

The second examination gave the following result:

Polymorphs	46.0 per cent.
Lymphocytes	39.0 "
Endothelial cells	13.0 "
Hyaline cells	0.5 "
Lymphoblasts (large lymphocytes)	1.5 "

Anisocytosis was present, punctate basophilia was slight, platelets were present. In a careful survey of two slides four nucleated red cells were seen, two normoblasts and two megaloblasts.

'The third count was done both by myself and by Dr. Price Jones, whose figures are as follows:

Polymorphs	53.9 per cent.
Lymphocytes	26.8 "
Large mononuclears	18.6 "
Eosinophils	0.4 "
Mast cells	0.3 "

1,000 cells were counted; 126 cells showed basophil granules, there was much polychromasia; 11 normoblasts and 2 megaloblasts were counted.

'These counts do not indicate any gross change in the relative numbers of white cells, for the lower polymorph count is explained by the age of the patient. The polychromasia, punctate basophilia, and nucleated red cells indicate activity of the bone-marrow, and the presence of megaloblasts in the last two counts suggests that this activity has increased since the previous counts. Normoblasts are not easily found even in moderately severe grades of pernicious anaemia, and megaloblasts in that disease are of serious omen.

'The details that have been published of the blood counts in the congenital cases have been examined, and careful scrutiny shows changes which, though slight, are distinct.

'Omitting the grave anaemia in Schumm's patient (Petry), the causation of which was known, only one case, that of Martenstein (15) (Case 11) showed a definite grade of anaemia in a deficiency of the red cells. The haemoglobin again, though somewhat low in most cases, is not below the normal for hospital patients. Of thirteen cases in which the colour index is either given or can be calculated, in six it is 1.0 or over. With a normal blood count of between four and five million cells the colour index is usually below 1.0, and the large proportion of higher indices can hardly be accidental.

'The appearance of the red cells frequently gives clear evidence of abnormality in the haemopoietic system which the count fails to show; anisocytosis, polychromasia, poikilocytosis, and punctate basophilia may all be present if carefully looked for. All these features are indications that the blood formation in the red marrow is hurried up and that immature cells are being discharged into the blood; they are familiar features in pernicious anaemia, in which we know that the red marrow is hypertrophied; they are absent or minimal in aplastic anaemia, in which the bone-marrow is not active. This reasoning is confirmed by the state of the bone-marrow of the sternum and femur in the post-mortem on Petry, where the marrow is described as deep red in all these situations; normally the marrow of the femur is fatty and not haemopoietic.

'Dr. Price Jones kindly examined slides from Garrod and Mackey's case, in December 1925, and wrote: "There is marked evidence of bone-marrow activity. There are polychromatic cells in every field. In a count of 500 white cells I counted ten red cells with basophil granules and two nucleated red cells, one a normoblast and the other a megaloblast. There seems to be a healthy number of platelets, certainly no excess such as I found in Dr. Gray's case. The same process seems to be going on in both the cases, i.e. exaggerated red blood cell production unassociated with anaemia."

'Not much attention has been paid to the presence of platelets; Price Jones noticed an excess in Gray's case; in slides from Mackey and Garrod's case and from Ashby's case they have been in normal amount. The corpuscular fragility tested in two cases (Garrod and Mackey and Günther) was found to be normal.

'The leucocyte count varies from 3,000 to 12,800, an average of 7,400, a figure rather above than below the normal blood count for hospital patients, though within the limits of 5,000 to 10,000 which are the extreme limits of normality for adults. The differential count in a large proportion of cases shows a diminution in the percentage of polymorphs, and an increase in the percentage of lymphocytes. Only in two cases, that of Radaeli and one of Martenstein's, is there a normal percentage (between 60 and 70) of polymorph cells, the remainder are between 46 and 58 per cent. If we take the absolute number of polymorphs per cubic millimetre as from 3,000 to 7,000, the average total in the recorded cases comes to 4,370.6 and the individual figures lie between the normal limits. The percentage of lymphocytes is on the average high and varies between 25 and 38 per cent. (normal 25 to 33 per cent.). The average absolute number of lymphocytes per cubic millimetre is 2,291.9 (normal 1,200 to 3,300). Therefore, while the low percentage of polymorphs and the high percentage of lymphocytes does not indicate any excess or diminution in these cells, we may probably relate it to the changes that are going on in the bone-marrow and especially in the spleen. Four instances have been recorded in which the endothelial cells are increased, which is again a suggestion of over-activity of the spleen.

'H. Günther (16) states that in the acute cases the cytological examination of the blood is normal except after loss of blood from some complication. On four occasions during an attack a polycythaemia has been present, in one case up to seven million red cells. W. Weigelt (17), in an examination of Günther's second acute case, using a method of vital staining of the blood, found granular (basophilic) cells in 1.3 per cent. of red cells during the attack and in 0.9 per cent. afterwards. He thence infers that both during and after the attack there is an

extra activity of the bone-marrow and an increase of immature cells in the blood, a conclusion which agrees with that for the congenital cases. Snapper's (18) case is the only one with a differential count with a polymorph percentage of 57 per cent. and lymphocyte of 33 per cent., which, though slightly abnormal, is not sufficient upon which to base any conclusion.

Even though there be excessive haemolysis in cases of congenital porphyrinuria, we need not necessarily assume that the haemoglobin of the broken-down corpuscles is the parent substance of the porphyrins excreted. Apart from the chemical difficulties which Fischer points out, it is conceivable that the destruction of red corpuscles may be a secondary event, due to the action of light upon sensitized blood in the peripheral circulation, analogous to the action of cold in paroxysmal haemoglobinuria. Red corpuscles, in suspension in normal saline, are readily destroyed by sunlight if a porphyrin be added to the liquid in which they float; and in blood-serum the destruction, although conspicuously restrained, is not abolished.

If a subject of the anomaly under discussion would consent to live, for a considerable period, in a feeble or artificial light, it might be possible to solve this and some other problems which it presents; for obviously we still have much to learn about the changes in the blood of congenital porphyrinurias.

The Enlargement of the Spleen and Liver.

It is highly probable that, in course of time, the spleen becomes enlarged in all cases of congenital porphyrinuria, but in some of the recorded cases no mention is made of that organ. In the original Schultz-Baumstark (19) case, which was diagnosed as *lepra bullosa*, the spleen of a man of 33 years reached below the umbilicus. When Petry was under Günther's observation, at the age of 18, his spleen was not palpable; five years later it was found to be large, and at the time of his death, at 32, was very large. In Hegler and Fraenkel's (20) case, of a woman aged 33, the spleen was enlarged, and as she suffered from tubercle was supposed, during her life, to be lardaceous. In Ehrmann's case, at the age of 50, the spleen is described by Robitschek as constantly palpable below the ribs.

In the young children it has not been enlarged. In the case of Cappelli's (21) patient, a boy aged 5, the splenic dullness extended from the seventh rib to the costal border; in Ashby's (22) patient, a girl of 3 years, the spleen is not palpable, and in our case it was not palpable at the age of 6, but at 8½ reached three inches below the ribs in the left nipple-line. Thus it is obvious that the amount of enlargement varies much in different cases, and that its onset is at different ages. The observed facts suggest that the splenomegaly is secondary rather than primary.

The few records of post-mortem examinations agree in noting the presence of large amounts of iron-containing pigment in the spleen, but little structural

change beyond some thickening of the capsule, and perhaps of the trabeculae. In the case of Petry we learn from the record of the autopsy which Professor Borst kindly allows us to quote, that the spleen weighed 1,450 grammes (48 ounces) and measured 25 cm. (10 inches) in the long axis. The pulp was soft, of a deep brown colour, and in it were old scars, some with necrotic areas of a brownish colour. The iron-reaction was strongly marked, the capsule was somewhat thickened and adherent to the diaphragm, and the trabecular framework was conspicuous. One is tempted to connect the splenomegaly with the abnormal blood picture, especially in view of the accumulation of iron in the organ, but such an explanation presents obvious difficulties.

Enlargement of the liver is a much less usual feature. It is mentioned in Hegler and Fraenkel's case (20) and it is stated that post-mortem much iron-pigment was present, especially in the Küpfer 'star cells', and also some iron-free pigment. Petry's liver was not seen below the costal arch when the abdomen was opened at the autopsy, and its surface was smooth. At a much earlier date Günther had found no failure of hepatic efficiency. We know of no case in which the liver was so much enlarged as in ours, unless in certain cases described by Radaeli (23), of doubtful congenital nature, and in which there were tuberculous lesions.

Perhaps the microscopic examination of Petry's organs will help to fill what is at present a gap in our knowledge.

The Pigmentation of the Bones.

One of the most striking features of congenital porphyria is the selective pigmentation of the bones of its subjects, which probably occurs in all cases of the anomaly. It presents the absolute antithesis of ochronosis, in which the cartilages are black, but the bony structures unstained. Such staining of bones has been recorded in not a few domestic animals, but we know nothing of the symptoms presented by the animals during life. Its extreme rarity in man bears witness to the rarity of congenital porphyria, for except in the recorded cases of that anomaly we have found no mention of such staining of bones in the course of an extensive search of records of post-mortem findings from Bonetus and Morgagni to the transactions of the old Pathological Society of London. Yet at the present time there are three known cases of the anomaly in England.

Another pigment has long been known to stain bones in a like selective fashion, namely alizarine, the pigment of madder root. This effect of feeding animals with madder was mentioned by a French writer, Antoine Mizaud (24), in the year 1572, and in 1736 it was investigated by a London surgeon named Belchier (25).

In 1798, Daniel Rutherford (26) of Edinburgh supplied the explanation of the selective staining limited to the calcareous structures, and showed that calcium phosphate acts as mordant, and holds the pigment by adsorption. He

found that when calcium chloride was dissolved in a solution of madder the precipitate of calcium phosphate thrown down on the addition of sodium phosphate carried down the pigment with it. The pigmentation by madder has been utilized by a number of investigators in the study of the development of the bones and teeth, and it has emerged clearly that it is in newly-formed bony tissue that the pigment is deposited. It is essentially a phenomenon of early life, and by intermittent feeding with madder alternate striae of stained and unstained bone have been obtained.

The porphyrins behave in the same way, although it appears that the several pigments of that group stain with very different degrees of avidity; and the method for the detection of porphyrin in urine, introduced by one of us (A. E. G.) more than thirty years ago, by precipitation on the phosphates thrown down by sodium hydrate, is based upon that fact.

Eugen Fraenkel (27) has carried out some most interesting researches by injection into rodents and dogs of porphyrins derived from the urine of Petry (mainly uroporphyrin) over considerable periods. He observed progressive pink coloration of the incisor teeth, and in very young animals pigmentation of the bones. The younger the animal and the more active the processes of growth the sooner pigmentation developed. In adult rodents only the incisor teeth, which grow continually, became coloured. In some cases the pigmentation of the teeth began on the fourth day, but the average period was twelve days. Even in adult animals the callus formed around a fracture stained deeply, whereas the rest of the bone escaped. By allowing periods of intermission of injections Fraenkel also obtained striation of long bones, from alternate deposition of coloured and uncoloured lime salts.

Schumm (28) concluded, from spectroscopic measurements, that in the bones of Fraenkel's patient which he examined the pigment present was uroporphyrin, and in the case of Petry, Hans Fischer (5) has proved conclusively that this was so. From the coloured bones he obtained uroporphyrin in crystalline form, whereas in the bone-marrow both pigments were present, but coproporphyrin predominated.

Moreover, Fischer has confirmed Fraenkel's results referred to above, by injection of uroporphyrin into animals, and showed that a single dose of 0.05 gm. of that pigment sufficed to colour the bones of a guinea-pig weighing 170 gm., whereas with repeated doses of coproporphyrin he got no staining. Hence he concludes that uroporphyrin has a special faculty of staining bones, and in this respect stands alone amongst pigments of its class. Lignac (29), who injected white mice with haematoporphyrin, also failed to obtain any staining of bones with that pigment.

On the other hand, the traces of coproporphyrin in normal urines are thrown down on a phosphate precipitate when a caustic alkali is added.

In this connexion some recent observations of Derrien (30) are of great interest. He has been carrying out an investigation of the red fluorescence of tissues, which is usually, if not always, due to porphyrins, and finds that in new-born animals, such as guinea-pigs and kittens, the parts of the skeleton

already ossified, and in guinea-pigs the teeth, show a ruby fluorescence, which contrasts strikingly with the bluish fluorescence of the cartilaginous portions of the bones. We should expect that here the pigment would be coproporphyrin, which indeed Derrien found in the amniotic fluid of ewes. That porphyrins play no unimportant part in antenatal metabolism is indicated by the long-known fact that meconium is rich in a pigment of that group, and indeed the antenatal meconium.

In our earlier paper we mentioned that we had been able to convince ourselves that the bones of G. L. were pigmented, by transillumination of his hands. E. Fraenkel (27) was unable to see such shadows in Petry's hands, although his bones were deeply stained. However, the deformities of his fingers must have made the examination difficult. As the difference can hardly be other than one of technique, and in order to determine the best method of carrying out such examinations, a number of experiments have been made by one of us (L. M.) who also aimed at showing what appearances are likely to result from pigmentation of the bones.

It was found that the best results were obtained when an electric bulb was enclosed in a wooden box, in the lid of which, and immediately above the lamp, a circular hole an inch and a half (4 cm.) in diameter had been cut. Over this hole a plate of glass was laid, and upon it the hand to be examined with the fingers as closely in apposition as possible. Various coloured glasses were tried, but, with the possible exception of one of ruby tint, none seemed to have any special advantage. The examinations were made in a dark room, after the eyes of the observers had become accustomed to the darkness.

In order to find out what appearances might be expected if the bones were coloured, rods of paraffin wax, 12 mm. in diameter, like candles without wicks, were used, and in some of them iron nails 6 mm. in diameter were enclosed. When examined by the above method, a cylinder with a nail in it appeared shaded throughout, but with a deeper but ill-defined central shadow. As the nail was withdrawn the wax behind it lighted up throughout its diameter. A piece of bone enclosed in a wax rod showed no shading, but if the bone were stained deeply with haematoxylin the central vague shadow and general shading were seen, as with the nail.

The fingers of the boy G. L. showed similar shadows. However, in order to have independent witness, the boy was brought to Oxford and was examined, by the same method, in the Clarendon (Physics) Laboratory, and we have the permission of Professor Lindemann, and of other workers in his Department, to say that they were convinced by what they saw.

Moreover, we are able to reproduce two excellent Lumière photographs taken by Dr. J. Brailsford of Birmingham, one of which (Fig. 1) shows the transilluminated fingers of a normal boy of ten years, and the other (Fig. 2) those of our patient G. L.

The usual technique was followed, viz. the dark room, a board with a circular aperture, and the glass plate to protect the hand. An A. G. F. A. coloured plate

was used, with no screen and with a lens-aperture of 4.5. The illumination was from the flash of 16.6 grm. (250 gr.) of A. G. F. A. flash powder held 15 cm. (6 inches) from the hand, which had previously been focussed.

It is interesting to note the absence of shadows in the normal fingers, the general shading and central shadows in those of G. L., and the clearer lines between the phalanges which had not been noticed in our naked-eye examinations.

The Pigmentation of the Teeth.

Our patient G. L. no longer stands alone among subjects of congenital porphyrinuria in exhibiting pigmentation of the teeth. A second case, that of a little girl aged $2\frac{1}{2}$ years, was recorded briefly by H. T. Ashby (22) in 1924 and will be described more fully by him. By the kindness of Dr. Ashby one of us (A. E. G.) was enabled to see this child, and can testify that the colour of the teeth is the same in the two children, but that the teeth of Dr. Ashby's patient are the more deeply pigmented.

The milk-teeth of G. L., of which some incisors have been shed, appeared much paler when dry than *in situ*, but regained much of their colour when wetted. To prepare sections of so small an object as a shed milk incisor obviously called for the highest skill in such matters, and accordingly we appealed to Mr. J. Howard Mummery, who most kindly made sections and reported on the appearances presented as follows:

'The tooth, a deciduous incisor, was shed naturally. The greater part of the root had been removed by absorption. It was divided longitudinally, with a fine saw, into two halves, ground down on a fine carborundum wheel on an electric lathe, and brought to the required thinness with the finger on a stone with water.

'The first half was washed and dried, treated for a moment with absolute alcohol, and mounted in euparal. In this section both the enamel and dentine showed a faint pinkish tinge, both before and after grinding, and there was a zone of strongly coloured dentine near the pulp cavity. The colour of the dentine appears to be in both dentinal tubules and matrix when examined under the microscope.

'The second half was prepared in the same manner, but treated with water only and dried, but was not mounted in any medium. At one stage of the grinding of this second section a rosy tinge was diffused throughout the dentine, and a coloured drawing was made before proceeding with the grinding. It was difficult to be certain that, in this preparation, the colour continued into the enamel, but there was a faint indication of its doing so at the enamel junction.'

When the boy came to Oxford we were enabled, by the kindness of Professor R. A. Peters, to examine him, with due precautions, in the dark room by the radiation of a mercury vapour lamp filtered through Wood's glass. His finger-nails and the scars left by the hydroa showed the usual silvery blue fluorescence, and the pigmented areas of his skin appeared black; but when his

teeth were brought into the path of the ultra-violet rays, they shone out with a brilliant pink light, of the same tint as the fluorescence of the urine. It was obvious that this method afforded a very delicate indication of the presence of porphyrins, as Derrien's observations, with which we were not then acquainted, show. In some adult subjects of the anomaly the roots of the teeth have been found to be deeply stained with porphyrin, whereas the crowns were not obviously coloured. It will be interesting to ascertain whether, in any such cases, the crowns show any trace of pink fluorescence.

The fluorescence test also promised to show whether the pigment was present in the enamel, or whether, as we at first supposed, and as Fraenkel suggested (27), the coloration of the teeth of these children was due to pigment in the dentine showing through the thin enamel of a child. The section of one of G. L.'s teeth, when examined with a lens in the invisible ultra-violet rays, showed a brilliant greenish fluorescence of the dentine, whereas the layer of enamel shone with the pink colour seen in the teeth *in situ*. In a section of a normal tooth the dentine showed a similar greenish light, but the enamel shone with a pale bluish fluorescence.

In order that the presence of porphyrin in the enamel should be placed beyond doubt, we asked Mr. J. E. Barnard to help us, and he most kindly examined a section of tooth, and demonstrated the appearance to one of us (A. E. G.) under his ultra-violet microscope arranged to give a fluorescent image.

The section mounted in glycerin, upon a selenite slide, was examined in the focus of the invisible ultra-violet rays, concentrated upon it by a series of quartz lenses. The picture presented was really beautiful. Around the pulp cavity the bright pink fluorescence of the pigmented zone of dentine was very striking. When the cutting edge of the tooth was brought into view, the enamel, front and back, emitted a brilliant rosy glow, and the intermediate acute-angled triangle of dentine shone with a pale blue light, and was traversed by two converging strips of pink. Presumably the pink fluorescence of the pigment in the dentine was masked by its inherent fluorescence. The effect could only be compared to a southern sunset. The structure of the enamel was faintly indicated, but the fluorescence appeared to be distributed with strict uniformity; there was no differentiation of prisms and connecting substance, no streaks to suggest infiltration, but rather evidence of uniform deposition of pigment upon the lime salts. The appearance favoured the view, for which there is much to be said, that the pigmentation of bones is due to actual laying down of adsorbed porphyrin with the calcium phosphate.

Why amongst the twenty or more recorded examples of congenital porphyria Ashby's patient and ours have alone shown conspicuous coloration of their teeth is a most interesting problem. In the case of Petry, Günther (16) described the crowns as yellow, but the roots were deeply stained; and in Hegler and Fraenkel's case (20) there was similar staining of the roots, but no discoloration of the crowns is mentioned.

Another patient who has come under observation in early childhood is the

boy of 5 described by Cappelli (21), who mentions the shape of the teeth, but says nothing about discoloration.

Again, no record suggests that the milk teeth of any of the adult patients had been coloured, whereas the permanent teeth were not; and in the case of G. L. such permanent teeth as have already been cut are hardly less deeply stained than those of the milk set. Presumably he will go through life with coloured teeth. The above facts, coupled with the presence of porphyrin in the enamel in our case, seem to dispose of the hypothesis which ascribes the colour to the thin enamel of the child.

A second possibility is that the teeth are pigmented in cases in which the anomaly makes its appearance at an unusually early age, indeed in intra-uterine life, when the enamel begins to be laid down. It is true that Ashby's case and ours are the only ones on record in which the redness of the urine could be traced back to the first days of life, and in both hydroa developed during the first summer; but such information is much more likely to be forthcoming from the mother of an affected child than from an adult patient, and there can be little doubt that other cases have been strictly congenital, nor that coloration of the bones supplies equally good evidence of that fact. No such pigmentation has been observed in acute fatal cases, even those in which there have been recurrent attacks of porphyrinuria, as in one recently described by H. Weiss (35). Although Fraenkel (27), in his experiments upon animals, found that the teeth became pigmented sooner than the bones, we know that the bones of human porphyrinurics may be dark brown, although the teeth show no obvious coloration.

A third explanation, and one which commends itself to us, is that the pigmentation of the teeth, as also of the bones, depends upon the *amount* of porphyrin, presumably of uroporphyrin, present in the organism at the time when they are being formed, a period which reaches back into foetal life; in other words, that it is a matter of dosage.

Undoubtedly there are wide differences of degree among cases of congenital porphyrinuria. In some cases, as in one of Anderson's (34), the red colour of the urine has been described as intermittent, or almost in abeyance at times; and the urine of the brothers described by Arzt and Hausmann (31) was never dark in colour. These variations cannot be wholly accounted for by the excretion at times of a colourless chromogen, and it is probable that our case and Ashby's are examples of a maximal degree of the anomaly. The early and pronounced enlargement of the spleen and liver of our patient lends countenance to this view. It is obvious that as regards dosage the conditions are not comparable with those of Fraenkel's experiments, in which, after injections covering periods of days and not of years, no pigmentation of the enamel could be detected. It has often been stated, from the time of Belchier (25) onwards, that in animals fed upon madder there is no coloration of the enamel, but, in a recent paper, Blotevogel (32) denies this, for when, in his experiments, large doses of alizarine were given the enamel of the animals was stained a deep pink colour.

Unfortunately we have been unable as yet to determine the nature of the porphyrin present in the teeth of our patient. One milk incisor was dissolved slowly in hydrochloric acid, but the tooth was very small and most of the pulp had been absorbed. In hydrochloric solution a pink fluorescence was seen, but no absorption bands.

Sodium acetate was added until the solution was acid with acetic acid, and it was shaken with a small quantity of chloroform and centrifugalized; but in order to avoid loss no attempt was made to get rid of precipitated lime salt. The chloroform layer showed no bands and was colourless; it yielded no fluorescence, whereas the pink fluorescence of the supernatant liquid showed that the porphyrin had not been taken up by the chloroform. All that can be said is that these results were to be expected if, as is almost certain, the pigment in the tooth were uroporphyrin. Later on, when more teeth are available, it may be possible to determine this point spectroscopically.

Possibilities of Palliative Treatment.

There would seem to be no doubt that the ultra-violet rays are the potent agents in the production of hydroa, and the most recent observations of Martenstein (15) confirm those of Freund and other earlier investigators on this point. The maximal effect is produced by waves shorter than any which reach us from the sun. On the other hand, that solar radiation produces hydroa in congenital porphyria admits of no doubt. It is extremely difficult to produce by artificial means an eruption like hydroa, and it would appear that long exposure plays an important part. Günther obtained an immediate brown pigmentation in Petry's case, after exposure of a small area of skin for four minutes to an arc-lamp of 19 amperes, with quartz lens and water-cooling, at a distance of 15 centimeters, and regards this 'Pigmentfrühreaktion' as an interesting diagnostic sign.

From some experiments made by one of us (L. M.) by exposure of small areas of skin to the light of a mercury vapour lamp, at a distance of 20 centimeters, it appeared that to radiations of such character and intensity, and for short exposures up to three minutes, the skin of G. L. was not more sensitive than that of a normal boy. After 24 hours a faint erythema appeared which persisted for a week, leaving a slight pigmentation. Of course, these experiments are in no way comparable to those of Günther.

Obviously any treatment which is likely to benefit the victim of this congenital and lifelong anomaly will aim at protecting him from the effects of light and actinic rays. The most obvious method, and one which is certainly efficacious, is avoidance of exposure to the harmful radiations, either by living in a subdued light and only going out after sunset, or by wearing a shady hat, gloves, and long stockings, methods which are irksome to a child. Whether by such means the development of visceral lesions and ultimate progressive anaemia can be averted we do not know.

Some patients acquire some natural protection from abnormal growth of hair,

and others from brown pigmentation, and application of a dark pigment to the exposed surfaces can hardly fail to help, but at a cost which sufferers do not willingly pay. The interesting researches of P. R. Peacock (33) on the use of fluorescent substances applied to the skin, which intercept the harmful rays and convert them into light rays before they reach the tissues, are full of promise. In our case a quinine ointment, made according to a prescription supplied by Dr. Ashby, is being applied, but it is too soon to estimate its value. This method produces no disfigurement and is easy of application, and, as Peacock points out, simple yellow vaseline, which is highly fluorescent, fulfils the requirements. White vaseline, on the other hand, is much less protective.

Another line of treatment which has been suggested aims at depriving the porphyrins of their sensitizing power, by bringing about their combination with metals. Fischer (5), who is pursuing most interesting investigations on turacin, and who found traces of such copper compounds of porphyrin in the tissues of Petry, suggests the administration of salts of copper, or of iron, to porphyrinurias. Lignac (29) has suggested the administration of calcium salts, such as the chloride; for he has found that the injection of calcium chloride into white mice rendered sensitive by porphyrin appeared to render the cutaneous lesions caused by light much less severe. He suggests that the calcium chloride should be given intravenously, but that method is hardly suitable for the treatment of a lifelong anomaly.

Whether or no such treatments prove effectual, we may confidently expect that by such simple measures as avoidance of exposure to bright light and the use of fluorescent ointments, future victims of congenital porphyrinuria will be spared the grave disfigurement and mutilations which have been the lot of such sufferers in the past.

Summary.

1. An account is given of the progress, during the past four years, of the boy whose case was described by us in our earlier paper on Congenital Porphyrinuria.
2. A report on the chemical examination of the urine and faeces, by Mr. E. N. Allott, shows that the pigments there present are of the same nature as those found by Hans Fischer in the case of Petry, namely, uroporphyrin, most abundantly present in the urine, and copro (sterco-) porphyrin in the faeces.
3. The blood picture of our patient is compared with those of other subjects of the anomaly.
4. The enlargement of the spleen and liver is discussed.
5. The technique of the demonstration of the coloration of the bones by transillumination is described, and photographic evidence is produced.
6. The value of the fluorescence test in the detection of porphyrin in the teeth is described, and the cause of the pigmentation of the teeth, in certain cases, is discussed.

7. Means of modifying the condition of the patients by treatment, and some suggested therapeutic measures are considered.

In conclusion, we desire to express our sincere thanks to those who have helped us in various ways: to Mr. Howard Mummery, Mr. J. E. Barnard, Drs. C. Price Jones, A. G. Gibson, and J. Brailsford, who have rendered most valuable aid; to Professors F. A. Lindemann and R. A. Peters, for facilities and advice; and to Professors Borst, Hans Fischer, and Hans Günther for most useful information and literature. We would also thank Drs. Gray and Ashby for opportunities of seeing the cases under their care.

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Fig. 2.
Fingers of G.L.



Fig. 1.
Fingers of normal boy of 10 years.
Transilluminated



HAEMATOPORPHYRIA CONGENITA (CONGENITAL PORPHYRINURIA): ITS ASSOCIATION WITH HYDROA VACCINIFORME AND PIGMENTATION OF THE TEETH¹

By HUGH T. ASHBY

THE condition of haematoporphyrin congenita is so very rare that each observed case should be put on record as material to serve for the construction of a clinical and pathological picture of this anomaly.

The following case is only the second in which the coloration of the teeth has been observed, and the fourth in which congenital porphyrinuria has come under observation in very early childhood.

We owe thanks to Günther for having recognized the existence of this rare inborn error of metabolism, and to Garrod for his keen interest in this and similar abnormalities. Mackey and Garrod reported the first case combining all the symptoms together with pink teeth.

The following case was shortly reported in the *British Medical Journal*, November 1, 1924, and I now wish to record a more detailed account of this case, together with its progress, which has been watched carefully for three years.

The child, M. M., came under observation at the Royal Manchester Children's Hospital at the age of twelve months (1923), and she has been under continuous observation to the present, when she is nearly four years of age.

The child was sent on account of the remarkable red coloration of the teeth, which had been noticed by Dr. Prentice. She is a well-grown child and mentally very bright. She is an only child of healthy English parents, and she has lived all her life in the town of Salford. There is no consanguinity of the parents, and no peculiarity of any kind can be traced in any member of the family on either side. The mother is an intelligent woman, and we can take her statements about the child before she came under observation as being correct. The child was breast-fed and has always thriven well. The mother is quite positive that the child's urine has always been of a port-wine colour, even from the first day, and that the napkins were stained red. This had gone on continuously from birth. The motions had been always dark in colour.

At the age of four months the parents took her away to the seaside for the annual holiday. The weather was hot and sunny. While away she came out with a rash on the face and back of the hands. The mother described the rash as being like large blisters, which were like chicken-pox, only larger. No other part of the body was affected. The blisters took many weeks to heal.

The case then came under observation and was fully investigated. She cut the first tooth at the age of six months, and it came through red in colour, rather

¹ Received Feb. 26, 1926.

darker than the gums. At the age of one year she had twelve teeth, all alike in colour, and the rest of the temporary teeth have been cut normally. The case was referred to Dr. Wigoder, L.D.S., who demonstrated its peculiarities at a meeting of the British Dental Society. No one of the members at the meeting had seen a similar case.

A tooth has been ground *in situ*, and the colour was as deep as the tooth could be ground, showing that the pigmentation is not superficial. She has not lost any teeth up to the present, so that it has not been possible to examine them further. During the last two years the teeth have become a shade darker in colour and they may now be described as being brown-pink.

The urine is normal in amount, and of a port-wine colour, which has never varied in intensity. There is no albumin and no blood has been present at any time.

I am indebted to Dr. A. Sellers for a spectroscopic examination of the urine, and to Mr. E. N. Allott for a report on the chemical nature of the pigments present in the urine and faeces. Mr. Allott writes:

'Two samples of urine and one of faeces from the above case were examined. These were all sent in glass jars without any preservative, and were examined immediately on arrival.

'Both specimens of urine were port-wine coloured, and on direct examination showed the two-banded "metallic" porphyrin spectrum. By the addition of acid, the ordinary "acid" spectrum of the porphyrin was clearly seen.

'The faeces, unlike the urine, presented no abnormality in appearance.

'The pigments were isolated from the material, and for further identification and purification were converted into their methyl esters. The product from the urine was obtained according to the directions of Fischer (*Zeit. Physiol. Chem.*, 1915, **95**, 148); that from the faeces was extracted by means of ether and glacial acetic acid, as described by Fischer and Schneller (*Zeit. Physiol. Chem.*, 1923, **130**, 311); the pigment was obtained from the hydrochloric acid solution by means of soda and sodium acetate, and was converted into the ester in the usual way.

'The porphyrin methyl esters had the melting-points 286° for the urine derivative, 245° for that from faeces. Both these values are somewhat lower than those given by Fischer (290° and $249-250^{\circ}$ respectively), but in conjunction with the absorption spectra are sufficient to identify the pigments with Fischer's "urinporphyrin" and "kot-(copro-)porphyrin".

'The spectra were measured on a calibrated Hartridge reversion micro-spectroscope, for the use of which I am indebted to Dr. Keilin. Fischer (*Zeit. Physiol. Chem.*, 1916, **97**, 125) used a simple Steinheil spectroscope, while Schumm (*Zeit. Physiol. Chem.*, 1917, **98**, 171), who made both photographic and visual observations, used a grating instrument.

'In this case also the bands seen in acid solution agree well with those of Fischer and Schumm: Schumm's bands IV and V were not seen; in alkaline solution the agreement is not quite so good.

'The results are tabulated below:

Uroporphyrin in N/10 Alkali (KOH).

Observer.					
E. N. A.	611.5	577.8	558.2	536.5	504.6
Fischer	609.5	571.5	557.0	536.5	502.5
Schumm	611.3		559.3	538.4	501.8

Coproporphyrin in N/10 Alkali (KOH).

E. N. A.	614.0	573.0	535.6	500.0
Fischer	616.5	569.0	534.0	501.0
Schumm	617.5	565.5	533.3	503.3

Uroporphyrin in Hydrochloric Acid.

				Strength of Acid.
E. N. A.	597.0	576.5	552.8	25 per cent.
Fischer	594.0	573.5	551.0	19 " "
Schumm	596.7	577.0	553.4	25 " "

Coproporphyrin in Hydrochloric Acid.

E. N. A.	594.0	572.8	549.4	25 " "
Fischer	592.0	570.0	548.0	19 " "
Schumm	593.1	573.5	549.9	25 " "

'No further attempt has been made, so far, in this case to estimate the output of porphyrin quantitatively in the urine and faeces, nor to prepare and identify any other porphyrin there may be present in subordinate amount. It is hoped to carry on a more detailed investigation on these points in the immediate future.'

The above results agree with those obtained in Mackey and Garrod's case, and, as in that case, the anomaly has been present even from the earliest days of life, and we can place complete reliance on the mother's statements, although the child was not seen until she was a year old. The urine has not been altered by diet as she has become older.

The blood, which has been examined from time to time, shows no anaemia. The red blood-cells have always kept normal in number and the haemoglobin percentage has been good. The following is an example of a blood count:

Red blood corpuscles	4,602,000
White blood corpuscles	5,900
Haemoglobin	85 per cent.

In view of the observations of Price Jones on the blood of Gray's patient with pernicious anaemia, in which he found evidence of excessive activity of the bone-marrow, I asked Dr. A. G. Gibson of Oxford, who has found similar evidence in the case described by Mackey and Garrod, to examine films from my patient. Dr. Gibson reports as follows:

'At a cursory glance the film appeared normal; but closer inspection under an immersion lens showed a large polychromatic cell in about every second field, punctate basophilia was detected after a careful search, and four nucleated red cells were seen on searching the slide systematically.'

The following is the differential count of 500 cells:

Polymorphs	39.0 per cent.
Small lymphocytes	34.4 "
Endothelials	15.4 "
Mast cells	0.2 "
Lymphoblasts	0.2 "
Neutrophil myelocytes	1.0 "

The red cells showed a slight anisocytosis and occasional punctate basophilia. Platelets were in moderate numbers; seven 'ghosts' of nucleated cells were seen and a careful survey of the slides showed four normoblasts. This would suggest some overaction of the bone-marrow, possibly with some slight grade of anaemia. The relatively high lymphocytic and low polymorph figures are probably due, as Dr. Ashby suggests, to the age of the patient ($3\frac{1}{2}$).

There is no enlargement of the spleen up to the present and the liver is also not increased in size. The fundi of the eyes are normal and there is no abnormal pigmentation in the eyes.

The bones have been fully investigated and quite clearly show that they are pigmented like the teeth. Difficulty was experienced at first in demonstrating this pigmentation, as when a small electric bulb is held in the hand, with the fingers clutched around it, only a diffuse red colour is seen. The bones are not visible by this method. Eventually, this difficulty was overcome. A wooden box $1\frac{1}{2} \times 1 \times 1$ ft. with a hole at one end to admit a powerful electric bulb was made. A small round hole $1\frac{1}{2}$ inches in diameter was cut in the top of the box, so that the light from the bulb inside the box was projected through the hole. The hand was then laid flat and firmly over the hole in a dark room and the bulb switched on. In this way bones show up from the surrounding tissues. The hands of many normal children have been used to demonstrate this and also to act as controls. The bones of M. M. show up quite definitely darker than the controls, as observed by independent witnesses. This darkness of the bones can only be explained by the deep colour of the bones of the hands. X-ray examination of the bones shows nothing abnormal, except that there is some delay in the ossification.

The skin. Attacks of hydroa vacciniforme occurred each summer during the child's first two years of life. Now that precautions, as indicated later, are taken, this danger has been much reduced and much scarring and disfigurement saved.

When the child, at the age of one year, was first seen there were two scars on the face, each about the size of a sixpence, and there were several smaller ones on the front of the knees. None of the scars were deep.

The child was taken away again to the seaside during the summer (1923), when the weather was exceptionally sunny and hot. While away she wore a small hat, a short dress, and socks, so that the knees and the upper part of the legs were bare and exposed to the sun. She had to be brought home on account of large blisters appearing on the face, hands, and legs. Directly after returning home she was brought to hospital again. The following was found: The face was markedly pigmented and sunburnt, and there were two large blisters on the cheeks. The back of the hands and fingers had many large blisters. The nails were also affected and were dark purple in colour, as if they had been severely bruised, and there were large confluent blisters on the front of both knees and upper legs. When an unburst blister was pricked, clear reddish fluid came out. The blisters took nearly six months to heal, even with careful protection and treatment. The site of the old blisters seems to remain sensitive to injury for some time after they have healed. Scars are left as the result of the blisters. The parts of the body protected by clothing have never been affected. Since that time great care has been taken to prevent further trouble of this kind, and the mother has been most painstaking.

There are no milium-like epidermis cysts on the pink areas left after the bullae have dried up, as described by Dr. Douglas Heath in Mackey and Garrod's case.

The effect of trauma on the normal skin is noticeable, and the child appears

to bruise easily after a fall or a blow. The bruise-marks persist longer than one would expect.

The child lives in Salford, a town well known for its smoky atmosphere, and where there is a minimum of direct sun. This is, without doubt, a great gain to the child. During the summer the mother only takes her out in the evening near sunset, and she is well protected by a large hat, long stockings, and gloves. On dull days she is taken out rather more, but always with the full protection of clothes.

Acting on a valuable suggestion made by Dr. Howitt, that quinine has the property of shutting out the ultra-violet rays, I have had a vanishing cream made by the Head Dispenser of the Royal Manchester Children's Hospital, who has taken great pains to find a satisfactory method of preparing this.

Quinine Skin Cream (Non-greasy).

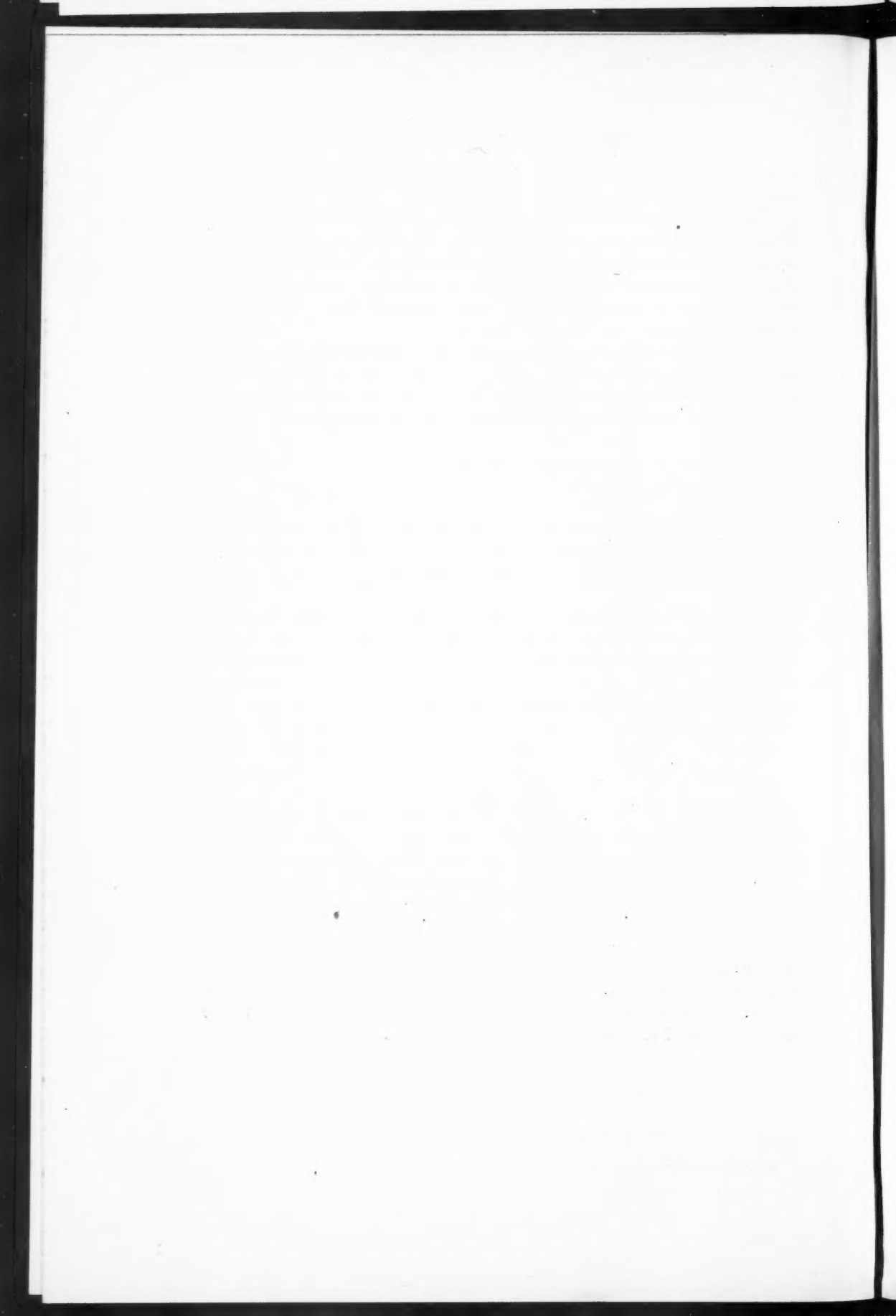
Rx Quinine (alkaloid)	5 grammes.
Acid oleic	20 "
Acid stearic	100 "
Pot. hydrox.	5 "
Aq. dist.	400 "

Dissolve the alkaloid in the oleic acid by aid of gentle heat. Add the stearic acid, and, when melted, add the hot solution of the pot. hydrox., while stirring briskly and maintaining a gentle heat for a little time. Colour—flesh-tint with cochineal.

As an alternative, a dusting powder may be used :

Rx Quin. sulphate	1 part.
Talc	15 parts.
Colour—flesh-tint.	

During this last summer I have tried the cream on M. M. and on other children, the latter being exposed to the direct sun while lying in the ward verandah. Half the face and body, one arm and one leg were covered with the cream, and the child then exposed to the sun for a definite time. This was repeated each day till slight sunburn was produced. The parts covered with the cream did not pigment, while the untreated parts pigmented normally, thus proving the protective power of the cream. The vanishing cream has been used by M. M. throughout last summer, and the mother is quite convinced that it has helped to protect the child. She has kept perfectly well and there have been no blisters. The cream is thus going to make the child's life more endurable, providing precautions with clothing are also carried out.



HAEMATOPORPHYRIA CONGENITA WITH HYDROA VACCINIFORME AND HIRSUTIES¹

By A. M. H. GRAY

(From the Skin Department, University College Hospital)

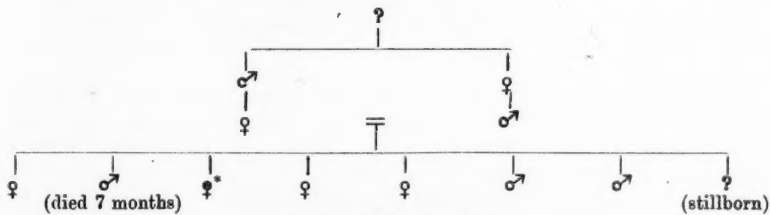
With Plate 29

CASES of haematoporphyrria congenita are of considerable rarity. Garrod, in 1923 (1), states that the known examples do not exceed twenty in number. It may, therefore, be worth putting on record an account of a patient suffering from this complaint, who has been under my observation during the last two years.

Case Record.

Ivy E., now aged 18 years, was first seen by me in November 1923. Her parents are first cousins, and are both living and quite healthy. She is one of a family of seven, having two brothers and four sisters, all alive and well. None of them has ever suffered from any skin eruption, nor have they ever passed any red urine.

Mr. Bolton King has kindly obtained the following family tree for me.



* The patient, Ivy E.

No history of any skin eruption is known in the family.

The child was apparently healthy till she was 5 years old, then, following an attack of measles in the summer, blisters came out on the face and hands, and, since that time, these have reappeared every summer and subsided again during the winter. At the time of the appearance of the first eruption it was noticed that the urine was of dark red colour. (The mother is very definite that it was never noticed before that age.) Since that date, however, the urine has always been of red colour, though the intensity of the redness has varied from time to time.

¹ Received February 26, 1926.

The eruption of blisters has recurred each summer up to the present time, and is localized to the face, neck, upper part of chest, backs of hands, forearms, and knees. No other area of the body had been affected until the summer of last year (1925), when a severe outbreak of blisters occurred on both legs and is attributed by the patient to the fact that, for the first time, she had been wearing thin silk stockings. Apart from this, the patient and her mother think that the eruption has not come out so severely in recent summers.

It has also been noticed that the blisters appear on the affected areas as a result of slight injuries.

The mother states that the patient is less well-developed, both physically and mentally, than the other members of the family, and that, apart from this complaint, her health has been quite good. She had whooping-cough as a baby and chicken-pox when about 10 years old. Also an attack of pleurisy in November 1924.

The patient was first seen by me in November 1923, and was admitted to University College Hospital for observation. She was again admitted for further observation in July 1925. In the intervals she had been living at home in Devonshire.

The patient is distinctly undersized and has very fair hair.

Skin. The skin all over the body is of a distinct yellow-brown (bistre) tinge and has a dry and lustreless appearance.

On the face the skin gives one the impression of being drawn rather tightly over the bones: there is little subcutaneous fat. The growth of hair on the face is very remarkable. The scalp hair extends downwards on the forehead to an unusually low level; the eyebrows are very thick and join each other in the middle line. Between the scalp margin and the eyebrows the forehead is covered with fine but long downy hairs. Similar long downy hair covers the cheeks, upper lip, and chin, and spreads down the sides of the neck to the upper part of the chest. On the nose there is very little growth of hair, though the lanugo hairs are perhaps a little thicker than normal. The downy hairs are particularly long and numerous in the malar regions, and both upper and lower eyelids are thickly covered with short fine hairs.

On the forehead, nose, cheeks, chin, neck, and upper chest are seen numerous small circular white scars; they are mostly about the size of a pea and very superficial. There is, however, a large and slightly deeper scar about the size of a sixpence in the centre of the forehead. Numerous small brownish pigmented macules (freckles) are also visible on the face, neck, and upper chest. The ears are only slightly affected.

The extensor aspects of the forearms are covered with thick downy hairs; the skin is freckled and shows numerous small superficial scars. The hands are curiously small, and the fingers stunted. The skin has a shrivelled appearance, is very much furrowed, though not abnormally thin. There is no excess of hair on the hands. There are numerous fine superficial scars on the backs of the hands and fingers, and numerous pinhead-sized milium bodies, chiefly seen on the dorsum of the first phalanges. The skin over the palms is flattened out, so that the hollow of the palm is less marked than in a normal individual.

The nails are normal, though there is a history of lesions having appeared under them.

A few small scattered scars are also present around both knees.

The above notes represent the condition of the skin as seen in November 1923; in addition, however, she had a linear deep-seated blister about $\frac{1}{2}$ inch long and containing blood-stained fluid on one finger. No further blisters developed while under observation at that time. The blister gradually dried up and formed a scab, which eventually fell off, the whole process taking three to four weeks.

When the patient again came under observation, in July 1923, numerous

thick blood-stained crusts were present on the face and upper chest, as seen in the photograph, and in addition there were several large crusted areas in front of both legs. All these crusted areas had been preceded by blisters. Two blisters only of small size on the right shoulder were present on admission, but none developed during her stay in hospital. It has been previously noted that this was the first outbreak of blisters on the legs, apart from the area surrounding the knees.

Conjunctivae. The conjunctivae do not appear to be abnormally pigmented.

Mouth and teeth. The teeth are of a deep yellowish-brown tint: the enamel is not deficient. The mucous membrane of the mouth shows no change. There is, however, a curious deep plum coloration of the mucous membrane covering the jaws immediately above and below the alveolar margins, possibly due to the staining of the bone beneath, as in this region the mucous membrane comes very close to the bone.

Mr. E. Bolton King was kind enough to examine the patient's teeth for fluorescence, and reports as follows:

'Her teeth fluoresced a white colour as do normal teeth, and there was no trace of the pink which was so prominent in those of the boy² whom I saw last summer. In fact the two cases are not at all comparable, as this one seems much milder—no active bad effects due to light, and the girl seems almost normal at present.'

Bones. On Sir Archibald Garrod's suggestion two attempts were made to determine increased density of the small bones of the hand by transillumination. The first attempt was made in 1923 with a small flash-lamp, and it was thought that a difference could be observed when compared with the normal individual. In 1925, however, a half-watt lamp enclosed in a box in which a hole about one inch in diameter had been pierced was used, and on this occasion there was no doubt as to the difference between the patients and the controls.

My House Physician, Miss Harmer, has made the following note: 'The patient's hand was examined by transillumination in a dark room. There was a distinct shadow down the middle of the fingers, while a normal hand used as a control showed no shadow.'

Viscera. Nothing abnormal was found on physical examination in the cardiovascular, respiratory, or nervous systems.

Neither liver nor spleen could be felt, nor was any enlargement of these regions discovered.

Dr. G. W. Goodhart, Clinical Pathologist to University College Hospital, kindly carried out an examination of the urine and faeces and also the blood-serum: his report is as follows:

Urine and faeces. Apart from the presence of porphyrin no abnormalities were detected in the stools, except that cysts of *lamblia intestinalis* were present from time to time. No red blood-cells, however, were ever seen.

'The amount of porphyrin in the urine, as measured by the colour of the urine and the amount recovered by precipitation with acetic acid, varied to some extent from time to time, and on the whole there was appreciably less throughout the period of the second admission to hospital than during the first stay. These variations, however, were insufficient to account for the very marked diminution that occurred in January 1924, during a period of mild pyrexia: for several days at this time the urine completely lost the dark red colour and showed only a faint pink tinge. It never was completely free from porphyrin, and always showed definite bands spectroscopically. The same fact was also noticed by Weiss (18).

'After precipitation with glacial acetic acid, the filtrate of the urine showed no bands by ordinary spectroscopic examination; it was, however, extremely dark in colour, and on some occasions the colour of the filtrate was practically

² The case of Garrod and Mackey.

indistinguishable from that of the original urine; as a rule, however, it had lost some of the red tint and appeared more definitely brown.

The spectroscopical examination of the urine and stools gave the following results, the figures given representing the middle lines of the bands in wavelengths measured with a direct-vision spectroscope.

Urine diluted 1 in 2	615.0	573.8	540.1	520
Urine treated with glacial acetic acid, filtered, and precipitate dissolved in 1 per cent. acid alcohol		597.3	558.5	
Stool treated with ether alcohol extracted with acetic acid ether		575.0	531.1	520

In order to compare the figures with Fischer's and Schumm's measurements, observations were made in 25 per cent. HCl and N/10.

Urine N/10 KOH	611.4	576.5	539.0	504.0
Stool N/10 KOH	620.0	576.5	541.0	507.0
Urine 25 per cent. HCl		595.1	558.0	
Stool 25 per cent. HCl		593.1	552.2	

The uroporphyrin was obtained by twice precipitating the urine with glacial acetic acid and extracting the precipitate with 25 per cent. hydrochloric acid. The copro- (stereo-) porphyrin was obtained by treating the entire stool with alcohol and ether: the mixture was filtered, and the filtrate extracted with acetic ether: the acetic-ether extract was washed ten times with water and the ether extract was then shaken out with 25 per cent. hydrochloric acid.

These findings show that the main urinary pigment is Fischer's uroporphyrin, whilst that from the faeces is copro- (stereo-) porphyrin.

Blood-serum. No porphyrin could be detected in the blood-serum, but the serum gave a positive indirect Van den Bergh reaction with $2\frac{1}{2}$ –3 units of bilirubin (January 23, 1924). The Wassermann reaction was negative.

A further examination into the corpuscular elements of the blood has been kindly made by Dr. Cecil Price-Jones of University College Hospital Medical School, who reports as follows:

When examined on 4. xii. 23, the blood-cell count gave 5,026,000 red cells, 102 per cent. Hb, a colour index of 1.02 + 5,500 white cells. There was no anaemia.

Examination of stained blood films to obtain a differential leucocyte count—which was quite healthy—showed a remarkable and unexpected condition. There was an enormous excess of platelets (not enumerated), a great number of the red cells were polychromatic, many contained basophile granules, and one normoblast was noted in a count of 300 white cells. Here then was a patient without anaemia, but with exaggeratedly active bone-marrow.

The degree of anisocytosis (variability) was 7.4 per cent., slightly greater than normal; the mean diameter of the red cells was 7.09μ , definitely smaller than the accepted mean of healthy persons; the distribution curve of the diameter was symmetrical and slightly shifted to the left. These findings closely resemble those of anaemia following haemorrhage.

To account for the apparent great activity of the bone-marrow in a blood in which there was no deficiency of red cells or haemoglobin, it was suggested that the bone-marrow was stimulated by the destruction of immature prehaemoglobinous red cells which were being produced in excess. This notion seemed to accord with the presence of porphyrin in the urine and stools—this porphyrin being not a haematoporphyrin derived from haemoglobin, but a coproporphyrin derived from cytochromes.

It was further suggested that the condition is the effect of light acting on a hypersensitive skin, increased erythropoiesis being a well-known action of sunlight.

'In Table I are given the figures of the blood examination taken at various dates up to 19.i.26.

'It is suggested that the patient is gradually becoming anaemic and the bone-marrow less able to compensate.

TABLE I.

Date.	Red Cells in Millions.	Hb %.	Colour Index.	Mean Diameter in μ .	Variability %.	Remarks.
4. xii. 23	5.026	102	1.02	7.09	7.4	1 normoblast in 300 w.c. Much basophilia and polychromasia; excessive number of platelets
13. xii. 23	5.500	106	0.96	6.90	7.8	1 normoblast in 300 w.c. Much basophilia and polychromasia; excessive number of platelets
10. i. 24	5.226	100	0.96	—	—	Fewer platelets; some polychromasia and basophilia; nucleated red cells not seen
22. i. 24	5.720	106	0.93	—	—	Excess of platelets; basophilia and polychromasia; no nucleated red cells seen
28. vii. 25	4.960	85	0.85	6.87	7.3	No excess of platelets; 11 nucleated red cells in 500 w.c., 3 being megaloblasts; 40 basophilic red cells, much polychromasia
31. vii. 25	4.690	82	0.88	6.82	7.7	No excess of platelets; 7 normoblasts, 2 megaloblasts in 500 w.c.; 50 basophilic red cells; much polychromasia
*19. i. 26	3.552	60	0.84	6.89	8.7	Excess of platelets; 8 normoblasts, 5 megaloblasts in 500 w.c.; 83 basophilic red cells; much polychromasia

* This count was kindly made for us by Dr. Solly of Exeter.

TABLE II.

Date.	White Cells per c.mm.	Lymphocytes %.	Large Mononuclear Cells %.	Polymorphs %.	Eosinophils %.	Mast Cells %.
4. xii. 23	5,500	31.0	6.6	61.0	0.3	1.0
13. xii. 23	7,200	25.0	15.0	59.3	0.6	0.0
10. i. 24	9,100	24.6	9.0	64.6	0.2	0.6
22. i. 24	11,000	34.2	9.0	55.2	1.2	0.4
28. vii. 25	12,000	31.8	13.2	53.4	1.2	0.4
31. vii. 25	7,000	33.6	9.0	55.8	1.0	0.6
19. i. 26	7,222	27.8	9.0	63.0	0.2	0.0

'In Table II are given the differential leucocyte counts, which are of healthy type and vary considerably; conceivably they are affected by the degree of hydrops present.'

Reactions to light. The patient was first under observation in midwinter, when any observations on the direct action of sunlight were impossible. On her second admission, in the summer of 1925, it was unfortunate that dull weather supervened, and although portions of skin were exposed to weak sunlight, no results were obtained.

Finsen-Reyn lamp. An area of skin was exposed at a distance of 10 cm. from the Finsen-Reyn lamp, without compression, for twenty minutes on December 18, 1923, and the same area for thirty minutes on December 22, 1923. No reaction resulted.

Kromayer lamp. An area of skin two inches in diameter was exposed to the water-cooled mercury vapour lamp on the following days:

Dec. 1, 1923.	25 cm. distance	5 minutes.
" 5, "	10 cm. "	5 "
" 23, "	10 cm. "	5 "
" 28, "	10 cm. "	10 "

No reaction appeared till the last exposure, when a patch of erythema resulted.

Further exposures to Kromayer lamp were made in 1925.

August 12, 1925. 10 cm. distance. 10 minutes to 2-inch area. Back of right forearm. Reaction: slight erythema.

August 13, 1925. 10 cm. distance. 20 minutes to 2-inch area. Back of left forearm. Reaction: erythema with two small blisters.

August 14, 1925. 10 cm. distance. 10 minutes to 2-inch area. Back of left arm. Reaction: slight erythema.

August 15, 1925. 10 cm. distance. 15 minutes to 2-inch area. Back of right arm. Reaction: erythema with one blister $\frac{1}{4}$ inch in diameter.

Controls taken from numerous other patients undergoing treatment with Kromayer lamp gave practically identical results.

Summary.

The points of special interest in this case are:

1. The relatively slight damage to the skin in spite of the fact that considerable quantities of porphyrin were generally present in the urine and faeces.
2. The fact that fluctuations occurred in the amount of porphyrin present in the urine, though at no time was it absent while the case was under observation.
3. The considerable diminution of the porphyrin in the urine during a mild febrile attack of unknown origin.
4. The absence of enlargement of the spleen.
5. The occurrence of considerable hirsuties on the exposed parts of the body.
6. The occurrence of blisters as a result of slight trauma, such as have been described by Douglas Heath in Garrod and Mackey's (17) case.
7. The evidence of marked blood-changes suggesting great activity of the bone-marrow.
8. The occurrence of a positive indirect van den Bergh's test.

Discussion.

The historical side of the question and the chemistry of haematoporphyrin have been so completely discussed by Sir Archibald Garrod (1) in this country, and by Günther and others abroad, that it is unnecessary to go into these questions here, even if one were competent to do so. There are, however, two aspects of this case which are of special interest to the dermatologist and which it may be

worth while briefly to consider, namely, (1) the question of the causation of hydroa occurring with porphyrinuria and where porphyrinuria has not been demonstrated, and (2) the question of hirsuties, which occurs in some of these cases.

Hydroa vacciniforme. *Hydroa vacciniforme* was first described by Bazin in 1862; since that date numerous cases have been recorded.

Hydroa vacciniforme is characterized by two main factors: (1) the appearance, on the parts of the body exposed to the direct light of the sun and during the spring and summer of the year, of blisters varying in size from a millet seed to a large pea, or larger if they coalesce, and (2) the formation of scars when the blisters heal. Although these lesions have been described on parts of the body other than the exposed parts, they have been few in number and their occurrence is extremely rare.

The production of blisters on the exposed parts, due to the action of the sun's rays, is not seen only in the above-mentioned condition, but may be seen occasionally in otherwise normal individuals whose skin has been exposed for an excessively long period to the sun's rays. The primary eruption in these cases is a diffuse erythema with swelling of the skin (erythema solare), and the blistering only occurs in the more severe cases. In some individuals who are abnormally sensitive to the sun's rays, however, this erythema and blistering may occur after relatively short exposures.

In 1879 Hutchinson (2) described the first of an interesting group of cases, which he named 'summer prurigo'. In these cases occurs an eruption of closely-set millet—to hemp-seed sized papules or papulo-vesicles on the parts exposed to sunlight during the spring and summer months. The eruption tends to clear up in the colder months of the year and to recur when the sunlight gets stronger. The rash itches a good deal and is scratched, and as a result minute scars are frequently left behind when the eruption fades. Hutchinson and others have described, under the same name, cases which are undoubtedly identical with Bazin's *hydroa vacciniforme*, and this has led to some confusion. Cases of Hutchinson's 'summer prurigo' undoubtedly develop blisters at times, but these do not usually give rise to scarring. Some authorities have differentiated these under a separate title of '*hydroa aestivale*', but this differentiation is not accepted by others. Hutchinson's cases are a much less well-defined group than those of Bazin, in that generalized cases occur, and also cases which persist throughout the year. Further, a group of cases with identical clinical features occur only in the winter, and have been spoken of as '*prurigo hiemalis*'. The lesions of Hutchinson's cases would seem to be of a more superficial character than those of *hydroa vacciniforme*, and would appear to be due to a chronic hypersensitivity of the surface epithelium, generally, though not always, to light.

It is still a matter of debate as to the relationship between the two conditions, and it is not proposed to enter here into a discussion on the subject; suffice it to say that it has been considered very fully by Adamson (3), and more recently by E. Pick (4), who take diametrically opposite views on the subject.

It is clear that the cases of Bazin's *hydroa vacciniforme* fall into two groups,

viz. : (1) those accompanied by porphyrinuria, and (2) those in which no porphyrin can be demonstrated in the urine. It is also clear from the classical experiments of Hausmann (5) on animals, and of Meyer-Betz (6) on himself, that haemato-porphyrin, when injected into the circulation, renders the skin highly sensitive to light, but in neither of these cases have lesions resembling those found in hydroa vacciniforme been produced. Meyer-Betz, after injecting 0.2 gm. of haemato-porphyrin into his blood, tried two different types of experiment. He exposed a small area of skin on one forearm to Finsen light, through a compressor, for three-quarters of an hour, and instead of getting a simple area of erythema surmounted by a blister, which would have been the reaction of a normal individual, he developed an area of complete skin necrosis, which eventually separated leaving a deep ulcer which took several weeks to heal. His second experiment was to expose himself to sunlight for a short period. This was followed by intense erythema solare with swelling of face and hands and superficial blistering, which, when it subsided, left no scars. The sensitiveness to light persisted in gradually diminishing degree for many weeks.

That certain of the sun's rays are responsible for the production of the lesions of hydroa vacciniforme can scarcely be questioned, for apart from the very definite history of the occurrence of the lesions as a direct result of exposure to the sun, characteristic hydroa lesions have been produced in subjects of this disease by exposure to various light sources. Freund (7) has found that hydroa lesions are produced with wave-lengths of 396-325 $\mu\mu$, while Funck (8) has got similar results with wave-lengths between 370-390 $\mu\mu$. Buquiechio (9), on the other hand, gets the most intense reaction from the indigo-blue rays. The skin of hydroa patients, both those with porphyrinuria and those without, shows a curious type of sensitiveness to light. The covered parts of the body do not react to single exposures of light more vigorously than normal individuals, the affected parts, however, appear to be hypersensitive to certain wave-lengths. Repeated exposures of the covered parts nevertheless appear to produce a hypersensitiveness in the treated areas.

There does not appear to be any clinical difference between cases of hydroa with porphyrinuria and those without this symptom. By far the larger number of cases described belong to the latter group, though it must be admitted that it is only recently that much care has been taken to examine the urine thoroughly. It must be remembered, however, that some authorities do not consider that uroporphyrin is responsible for the production of hydroa, but rather the presence of porphyrinogen or of stercoporphylin in the blood. It is probable that the same attention has not been paid to the estimation of porphyrin in the faeces as is the case with the urine. That cases do occur without any abnormality in the urine, and with only a trace of porphyrin in the faeces, not more than might be found in any normal child, is shown by a case of typical hydroa now under my own care, whose urine and faeces were carefully examined by Dr. G. A. Harrison, the Bio-chemist to the Hospital for Sick Children, Great Ormond Street.

The histology of the lesions in the two types of case appears to be identical,

the more pronounced lesions showing a definite tissue necrosis extending down in the corium almost to the subcutaneous tissue and involving also the overlying epidermis. The lesions suggest that the light effect is felt chiefly on the vessels of the corium, and that we are not dealing with a hypersensitiveness of the epithelial cells, such as appears to be the case in erythema solare and in Hutchinson's summer prurigo.

The question one asks oneself now is whether there is sufficient evidence to show that the sensitiveness to light which produces these hydroa lesions is really due to porphyrin. To my mind the evidence is not at all clear. First, the experimental lesions have no resemblance to those which occur in hydroa. In Meyer-Betz's (6) experiments the eruption was of the type of an erythema solare, probably due to a sensitization of the surface epithelial cell. This type of sensitiveness apparently does not occur in hydroa patients, witness the failure to obtain reactions on the covered parts of the body.

With regard to the Finsen experiment by the same observer, Buquicchio (9) exposed an area of skin of a hydroa patient (without porphyrinuria) to the Finsen lamp, presumably, though it is not definitely stated, with compression, for ten minutes. He observed an immediate erythema, followed rapidly by blister formation, and erythemato-bullous dermatitis. Here the reaction does not appear to be of the nature of a hydroa, as no reference is made to scar formation. Martenstein (10), in a porphyrinuria patient, and Funck (8), in a non-porphyrinuria patient, obtained practically no reaction by exposure to the Finsen lamp without compression, and this corresponds to my own case, but the absence of compression obviously prevented the penetration of the rays to the same degree as if compression had been used. Nevertheless, the Meyer-Betz experiment with the Finsen lamp does suggest a sensitiveness of the deeper vessels.

Then hydroa does not occur in those groups of porphyrinuria named by Günther (11) 'acute' and 'acute toxic', while the three cases in Günther's 'chronic' group probably, as Garrod points out, belong to the 'congenital' group.

Even in cases of haematoporphyrin congenita hydroa does not always occur, as in Hegler, Fraenkel, and Schumm's case (12).

Further, it is recognized that the amount of porphyrin in the urine bears no relation to the severity of the attacks of hydroa. This, however, is an observation of small importance when it is remembered that many severe cases occur without any appreciable porphyrin in urine or faeces. In this connexion it may be worth quoting from Meyer-Betz: 'It (haematoporphyrin) need not of course necessarily appear in the urine. In my experiments with an intravenous injection of 0.2 grm. of haematoporphyrin there were doubtless quantities of it in the blood-stream at one time such as would scarcely ever occur under natural conditions. The 300 c.c. injected formed a deep brown solution, *whereas in the urine only minimal quantities were excreted*. There is nothing against the assumption that in cases of hydroa, where no haematoporphyrinuria occurs, this is yet present in the skin, while other cases obviously occur where haematoporphyrin is formed in large quantities, but for some reason or other there is no

formation of blisters (Hegler, Fraenkel, and Schumm's case). In any case only minimal quantities are sufficient to produce sensitization. . . .

Taking all these facts into consideration, it does not appear to be proved that the sensitiveness to light which underlies the production of hydroa lesion is necessarily due to the porphyrins even in the haematoporphyrin cases, still less in those with no haematoporphyrin.

There is another point of great importance in hydroa cases—that is, the tendency to occur in families. Siemens (13) has collected ten family groups, some being haematoporphyrin cases and others not. He estimates that some 10 per cent. of the published cases of hydroa have some family history. This suggests a similarity with cases of epidermolysis bullosa, in which the family history is even more marked. In this latter disease very similar lesions are produced on slight trauma. Presumably a congenital sensitiveness to trauma exists in the cells, and particularly in the cells of the blood-vessels of the dermis, as from histological examination the lesions appear to commence in this region. Is it not possible that a similar congenital sensitiveness to short wave-length, rays of light exists in hydroa vacciniforme, without having to invoke the theory of chemical sensitization?

It is possible that the scattered arrangement of the lesions in hydroa may be due to the varying thickness of the epithelium overlying the superficial dermic vessels. When it is remembered that the short wave-length rays, namely, those which have been shown to produce hydroa lesions, have little penetrating power, it is conceivable that slight increases in thickness of the epidermis may prevent these reaching the sensitive vascular endothelium. Greater epidermal thickening may also account for the lessening of the tendency to hydroa lesions when adult life is reached.

In this case it is possible that the porphyrin is produced also by the action of light on the blood-cells, as suggested by Price-Jones in his note on the blood picture of the case described above, and may go some way to explaining the increase in colour of the urine during attacks noted by McCall Anderson (14), and after exposure to light by Radaeli and Linser (quoted by Garrod (1)).

Hirsuties. The *hirsuties* which occurs occasionally in cases of haematoporphyrin is of great interest, but little can be said about it. In addition to the case recorded above, only two other cases of this type are on record, those of Cappelli (15) and Arzt and Hausmann (16). In Cappelli's case the hair seems to have been thicker and longer on the forehead than in my case, but the distribution was not so extensive. In Arzt and Hausmann's case, the younger of two brothers both suffering from the same condition, the forehead was hairy; fine, soft, downy hairs covered the eyelids. The eyebrows were extraordinarily long.

In the case of Hegler, Fraenkel, and Schumm (12) the patient was a 'bearded woman', and the type of *hirsuties* in her case was entirely different to those in the three cases above mentioned, and was similar in type to other cases not associated with haematoporphyrin or hydroa.

In my case, more than in others, almost the whole of the parts affected by

the hydroa lesions was involved, the only exception being the back of the hands and fingers, while the nose was less affected than other parts of the face.

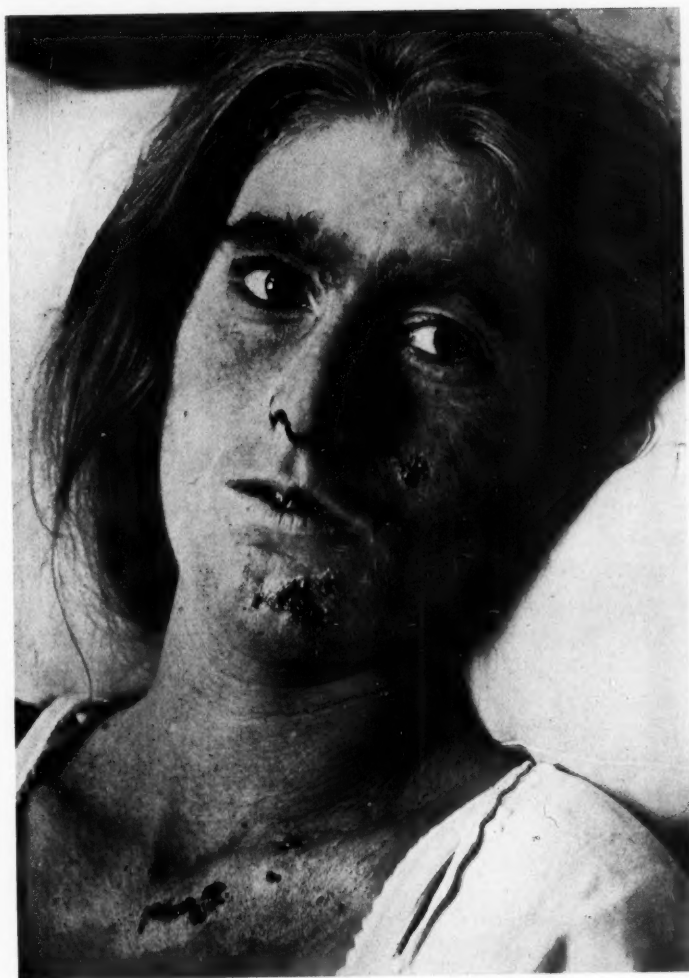
This type of hirsuties does not correspond to any of the described types. On the one hand, excessive downy growth is known to occur frequently on sites of skin irritation. Presumably our cases must be looked upon as belonging to this class. The excessive hair production is probably protective. On the other hand, it is extraordinary that if this is the case, it does not occur with greater frequency. It is possible that there must be some constitutional tendency to the hairiness, which is presumably not common, to predispose to this effect of light. This view is borne out in my case by the extremely low growth of the scalp hair, the thickness of the eyebrows, and the tendency to meet in the middle line, conditions which are sometimes met with in otherwise normal individuals. Also in Cappelli and in Arzt and Hausmann's cases, the excessive length of the eyebrows was noted.³ These can scarcely be a protective overgrowth, nor can it be due to local skin irritation, as these areas are well protected from light.

In compiling this paper, I am much indebted to Dr. Goodhardt for his examination of the urine and faeces, to Dr. Price-Jones for his investigation of the blood, and to Dr. J. W. McNee for doing the van den Bergh test. Also to Mr. Bolton King, who was kind enough to go from Oxford to Exeter to investigate the fluorescence of the teeth, and to Dr. F. A. Roper, of Exeter, who is now in charge of the patient, for various notes of the case. I am, however, especially indebted to Sir Archibald Garrod for giving me information on many points and giving me access to his notes and books dealing with the subject.

³ Günther in a recent article on Haematoporphyria (*Enzyklopädie der klinischen Medizin, Handbuch der Krankheiten des Blutes u. der blutbildenden Organe*, 1925, ii. 668) points out that anomalies of hair development in these cases is not uncommon. One of his cases had thick eyebrows meeting in the midline and another had long dark eyelashes.

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THE DEXTROSE TOLERANCE CURVE IN HEALTH^{1, 2}

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FOR many years it has been known that after giving dextrose by the mouth there is a rise in the sugar-content of the blood, and that this rise is greater in a diabetic than in a normal person. More recently, with the increase in ease and accuracy with which the blood-sugar can be estimated, 'sugar tolerance curves' have come into use as an aid to diagnosis in many diseases in which errors of metabolism are suspected. Up to the present time there appears to be a certain lack of agreement as to the significance of the various findings. This is due in part to the different methods of performing the test adopted by various workers, and in part to an insufficient appreciation of the variations in the curve that may be found in health. It was therefore thought that the sugar-tolerance curve in health was worthy of further study, and that the results obtained might prove of value in discussing the results of the test in various diseases.

The first part of this paper is devoted to the study of the technique of the test. Our experimental results are then given, and these are followed by a discussion thereon. The curves from healthy subjects are given at the end of the paper.

Technique.

The duration of the fast. Before the test is begun a sufficient period of starvation must be allowed for the blood-sugar to return to normal after the previous meal. Although four hours should be long enough for this purpose, it is usually found convenient to begin the test in the morning, after starvation since the previous evening meal. It has been shown that even when a subject is starving the blood-sugar varies at different times of day. By always starting the test at the same time this difficulty is overcome.

The dose of dextrose. Perhaps the greatest variation in the many reported series of tolerance tests is in the matter of the dose. Many American and some

¹ Received Jan. 29, 1926.

² A part of this paper was incorporated in a thesis for the degree of Doctor of Medicine at the University of Cambridge by one of us (R. H.-W.). A part of the expenses was defrayed out of the Parsons' Research Fund, and the work was carried out during the tenure by one of us (W. W. P.) of the Parsons' Research Fellowship.

(C. J. M., April, 1926.)

Continental workers use a standard dose of 100 grm. dissolved in varying amounts of water. Others give 1.75 grm. per kilo body-weight. Only a few have used smaller doses. In England it is more usual to give 50 grm., and in the more recent Scandinavian work a dose of 1 grm. per kilo. body-weight is given, which generally results in a dose not greatly in excess of the usual English one.

According to MacLean (1) and also to M. Hansen (2), doses of dextrose above 25 grm., when given to normal persons, do not cause a greater rise in the blood-sugar than 25 grm. would, but merely delay its return to normal. If this view is correct, as the duration of the rise is just as important as its height, the giving of a larger dose than is necessary to obtain the maximum height only prolongs the time required to complete the test. The observations of MacLean and M. Hansen are not altogether confirmed by Hagedorn (3), who find a higher rise with a larger dose. A similar result is shown in the following readings, all obtained from the same person by one of us :

Dose of Dextrose. Grm.	Blood-sugar before taking Dextrose.	Blood-sugar after Dextrose.				
		$\frac{1}{2}$ Hour.	$\frac{3}{4}$ Hour.	1 Hour.	1 $\frac{1}{2}$ Hours.	3 Hours.
25	0.105	—	0.130	—	0.105	0.107
50	0.102	0.165	—	0.155	0.079	0.110
100	0.103	—	0.220	—	0.165	—

But many published results show that the increase in rise with an increase in dose is not constant enough to warrant the routine use of a dose as large as 100 grm. Large doses of sugar prolong the experiment, and may be actually harmful in cases of diabetes; indeed, some authors go so far as to suggest that they may be harmful to a normal individual (4). Moreover, so large a dose as 100 grm. is distinctly unpleasant to take and often causes nausea, which has a disturbing effect on a sugar-tolerance curve.

The source of blood. It has been shown by Hagedorn (3) and confirmed by many subsequent workers that, after the ingestion of dextrose, the sugar-content of venous blood is often definitely less than that of 'capillary' blood. The following few examples from Hagedorn's work of blood-sugar determinations on samples of venous and capillary blood obtained simultaneously will show the importance of this difference :

Blood-sugar % Capillary Blood	0.204	0.157	0.148	0.159	0.122
" " Venous Blood	0.169	0.118	0.110	0.112	0.097

Thus the height of the rise varies considerably according to the source of blood. It is of interest to note that this difference decreases or disappears entirely in diabetes (3, 5, and 6).

The Danish workers use capillary blood and the Americans venous blood; this accounts for the observation of many American writers (e.g. Folin and Berglund (7)) that the figures obtained by Jacobsen and other Danish workers are higher than their own.

It has been suggested that obtaining blood from the finger-tip is more painful than venapuncture. We have only one patient, among those on whom both

methods have been used, who preferred venapuncture. Pricking the finger is a very much simpler procedure, especially if several samples of blood have to be taken.

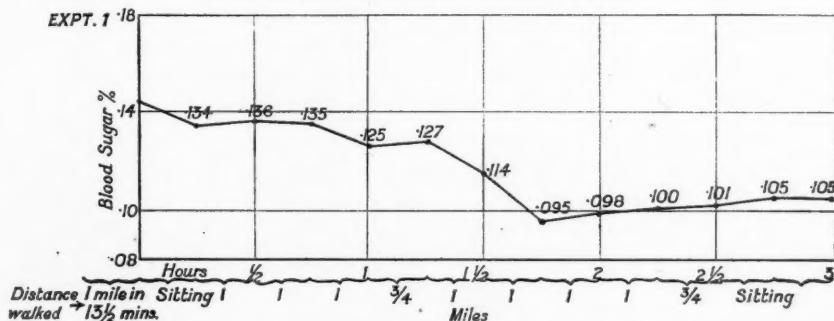
Time of taking samples of blood. The time of taking samples depends entirely on what information is desired from the test. As will be shown later, the sugar-content of the blood is liable to such rapid variations that it is impossible to establish the exact height of the peak of the curve or the time of its occurrence. But as our present purpose is to make the investigation of the sugar-tolerance curve in health as accurate as is practicable, a near approximation of the height and time of the peak must be obtained, and therefore samples of blood were taken every fifteen minutes for the first $1\frac{1}{2}$ hours.

The other important feature we have tried to establish is the time taken for the blood-sugar to return to normal, and for this purpose samples should be taken for $2\frac{1}{2}$ hours at least.

The effect of exercise. As it is not always convenient to keep subjects in bed before and during the test, the following experiment was undertaken to ascertain the effect of exercise on the blood-sugar :

Experiment 1.—Subject 1 (W. W. P.). After the usual night's fast he walked 1 mile in $13\frac{1}{2}$ minutes before taking the glucose. In the first $\frac{1}{4}$ hour after taking the glucose he took no exercise to avoid the possibility of nausea. Between $\frac{1}{4}$ hour and $2\frac{1}{2}$ hours samples of blood were taken every $\frac{1}{4}$ hour, and between each sample he walked 1 mile, except on two occasions when he only walked $\frac{1}{2}$ of a mile. The taking of samples took about $2\frac{1}{2}$ minutes.

Experiment 1 (Subject W. W. P.)
Walking exercise taken before and during the test.



It will be seen by comparing this result with the same subject's curves obtained under normal conditions (Nos. 1, 2, and 3 in the Appendix), that by walking 1 mile in $13\frac{1}{2}$ minutes the fasting blood-sugar was raised to 0.144 per cent., and that 50 grm. of glucose failed to produce the usual rise, but, instead, the blood-sugar fell slowly to 0.095 per cent. at $1\frac{1}{2}$ hours. This is only a single experiment, but it is quite enough to show that if the subject cannot be kept in bed during the test, at least his exercise must be reduced to a minimum.

In curve 7 from subject 3 (see Appendix) we find a fasting blood-sugar

of 0.124 per cent. This man was known to have hurried to hospital as he was late. It would seem, therefore, that a rest of a few minutes should be insisted on before the zero sample is taken.

Method of analysis. Comparisons between various methods of analysis reveal a fair amount of agreement. The iodometric titration methods all agree (Bang's micro method, MacLean's, Hagedorn and Jensen's, and Shaffer and Hartman's). Folin and Wu's colorimetric method gives slightly higher results, especially for quantities below 0.1 per cent., but otherwise is in good agreement. The Lewis-Benedict colorimetric method, while often giving concordant results, frequently gives quite marked differences (see Høst and Hatlehol (9)). It is thus somewhat difficult to compare the work of authors using venous blood and the Lewis-Benedict method with that of those using capillary blood and some of the other methods.

The method used here is that of Folin and Wu (16), modified to require only 0.2 c.c. of blood. The error of this modification has been found by us to be only ± 0.003 per cent., and therefore it has seemed advisable to give readings to the third place of decimals.

All these factors, viz. the duration of the fast, the dose of dextrose, the source of blood, and the time of taking it, exercise, and the method of analysis, are capable of control, and clearly all must be standardized before results can be compared.

Experimental Results.

In selecting subjects for the formation of normal standards, it has been thought inadvisable to take patients from either the medical or the surgical wards of a hospital. Material for the study of the sugar tolerance curves in young adults is available among the students and laboratory workers. Greater difficulty is found in obtaining subjects for the investigation of the changes in the curve due to age, and this probably accounts for the scantiness of the literature on this important subject. We have been fortunate, through the kindness of the authorities at Lambeth Hospital, in being able to obtain a group of volunteers over 60 years of age from among the healthy inmates of the work-house wards.

Our results have been placed in two tables. In Table I all the subjects were young male adults under 30, and in Table II they were all over 60 years of age.

In each experiment 50 grm. of dextrose dissolved in 100 c.c. tap-water were given by the mouth. In no case was sugar found in the urine previous to the experiment, but in samples of urine collected two hours after the giving of the dextrose a trace of sugar was found in the case of subjects 17 and 25.

It will be observed from Tables I and II that, apart from the difference due to age, there are considerable variations to be found among the members of each group, and also that individuals do not give the same type of curve on different days. These differences are shown both in the rate and height of the rise and the time taken for the blood-sugar to return to normal. Some factors which may cause these variations in the sugar tolerance curve are considered under the following headings.

A. *The psychological element.* It has long been recognized that excitement and apprehension may cause a rise in the blood-sugar. It is worthy of note that in four of the six students, on whom duplicate tolerance tests were performed, the fasting blood-sugar in the second test was definitely the lower. It will also be noticed that curves 1 to 7 (from subjects 1 to 3) show less variation from each other than curves 8 to 21 (from subjects 4 to 11). Curves 1 to 7 are from laboratory workers, and curves 8 to 21 are from medical students, who are always found to be apprehensive in a test of this kind lest it should reveal some abnormality.

Curve 30 in Table II is very striking. It is of interest that this subject was the only one who showed any resentment to the test. It was very desirable to have a duplicate curve in his case, but he could not be persuaded to have this done.

There are various other peculiarities in some of the curves which can be most conveniently explained by attributing them to the psychological attitude of the individual to the test, but it is impossible to say to what extent such an explanation would, in each case, be just.

B. *The rate of emptying the stomach.* In an attempt to interpret sugar tolerance curves, such an important variable as the rate of emptying the stomach cannot be omitted from consideration. Some workers (e. g. Woodyatt, Wilder, and Sansum (10)) have considered the rate of emptying the stomach to be of such significance that they have preferred the intravenous injection of glucose to giving it by mouth. Others (e. g. K. M. Hansen (2)) believe it too unimportant to deserve attention.

We have approached the study of this matter by means of the following experiments:

Experiments 2 and 3. 50 gm. of dextrose mixed with a suspension of barium sulphate were given to a fasting student, and the rate of emptying of the stomach was followed by means of X-rays. Blood was taken for sugar estimation at each inspection. The experiment was repeated with the addition of 130 c.c. of olive oil to delay the emptying of the stomach.

The results were, however, inconclusive, and this method was abandoned as being too far removed from the normal conditions to be satisfactory.

Experiments 4, 5, 6, and 7. (Subjects 1 (W. W. P.) and 2 (R. H.-W.)) In each experiment an Einhorn tube was swallowed and 50 gm. of dextrose were then taken by the mouth. In experiments 4 and 5 the dextrose was dissolved in 100 c.c. water, and in experiments 6 and 7 in 500 c.c. Samples of blood for

TABLE I. *Sugar Tolerance Curves from Healthy Young Male Adults.*

Sub- ject No.	Curve No.	Time in Hours.									
		0	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{3}{4}$	1	$1\frac{1}{4}$	$1\frac{1}{2}$	2	$2\frac{1}{4}$	$2\frac{1}{2}$
1	1	0-114	0-102	0-175	0-159	0-141	0-145	0-117	—	—	0-111
	2	0-112	0-137	0-157	0-151	0-132	0-144	0-108	—	—	0-100
	3	0-116	0-133	0-176	0-163	0-160	0-145	0-118	0-102	—	0-115
2	4	0-115	0-127	0-166	0-175	0-155	—	0-125	—	—	0-100
	5	0-112	0-144	0-178	0-164	0-138	0-125	0-113	0-104	—	0-099
	6	0-115	0-157	0-146	0-129	0-141	0-146	0-153	0-114	—	0-103
3	7	0-124	0-155	0-178	0-151	0-141	0-134	0-105	0-100	—	0-115
	8	0-118	0-168	0-097	0-118	0-122	0-128	0-139	0-136	—	0-108
4	9	0-099	0-126	0-112	0-131	0-115	0-126	0-113	0-140	—	0-100
	10	0-118	0-120	0-151	0-162	0-148	0-130	0-128	0-118	—	0-100
	11	0-118	0-113	0-128	0-144	0-151	0-139	0-125	0-131	—	0-119
6	12	0-124	0-122	0-132	0-152	0-140	0-122	0-116	0-133	—	0-107
	13	0-100	0-131	0-138	0-134	0-117	0-125	0-122	0-114	—	0-101
	14	0-118	0-119	0-129	0-139	0-135	0-138	0-145	0-149	—	0-131
7	15	0-123	0-128	0-162	0-153	0-150	0-157	0-153	0-169	—	0-132
	16	0-114	0-138	0-150	0-203	0-150	0-126	0-124	0-140	—	0-092
8	17	0-098	0-143	0-164	0-136	0-116	0-104	0-089	0-101	—	—
	18	0-116	0-157	0-189	0-191	0-157	0-161	0-135	0-127	—	0-097
9	19	0-104	0-148	0-170	0-170	0-138	0-121	0-107	0-098	—	0-096
	20	0-108	0-134	0-182	0-197	0-180	0-169	0-134	0-122	—	0-097
11	21	0-101	0-131	0-192	0-187	0-170	0-141	0-123	0-146	—	0-078

TABLE II. *Sugar Tolerance Curves from Subjects over 60 Years of Age.*
(Arranged in order according to age.)

Sub- ject No.	Sex.	Age.	0	Time in Hours.					3
				$\frac{1}{2}$	$1\frac{1}{4}$	$1\frac{1}{2}$	$1\frac{3}{4}$	2	
12	M	67	0.123	0.181	0.163	—	0.120	—	0.110
13	F	67	0.091	0.168	—	0.183	—	0.118	—
14	M	68	0.090	0.116	0.150	—	0.138	—	0.156
15	M	69	0.098	0.164	0.132	—	0.133	0.126	0.085
16	M	71	0.108	0.179	0.212	—	0.220	0.140	0.110
17	M	72	0.110	0.220	0.174	—	0.156	0.140	0.089
18	M	73	0.103	0.152	0.152	—	0.139	0.115	0.110
19	M	74	0.098	0.152	0.158	—	0.168	0.111	0.121
20	M	75	0.147	0.145	0.146	—	0.129	0.133	0.098
21	F	76	0.106	0.164	—	0.168	—	0.128	0.114
22	M	76	0.130	0.202	0.178	—	0.150	—	—
23	M	77	0.098.	0.135	0.167	—	0.224	0.177	0.097
24	M	78	0.119	0.187	0.240	—	0.184	0.193	0.101
25	F	98	0.112	0.275	—	0.310	0.196	0.115	0.086
							0.282	—	0.155

sugar estimation were taken every $\frac{1}{4}$ hour, and at the same time small amounts of the gastric contents were removed for analysis.

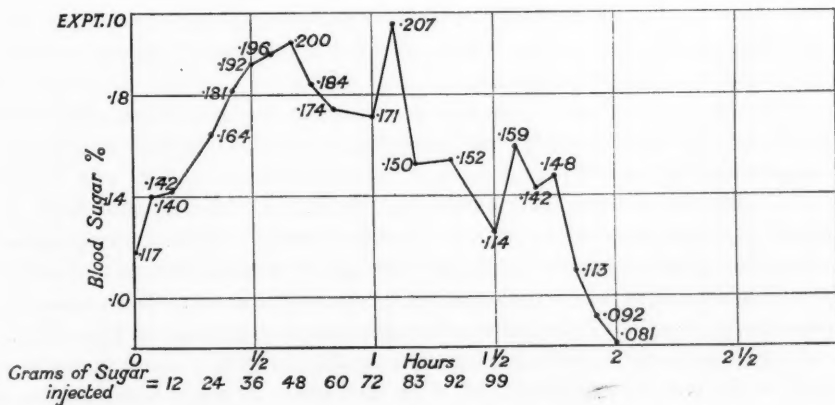
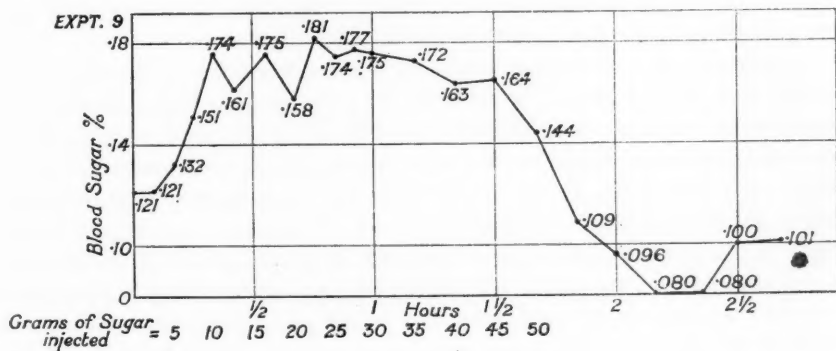
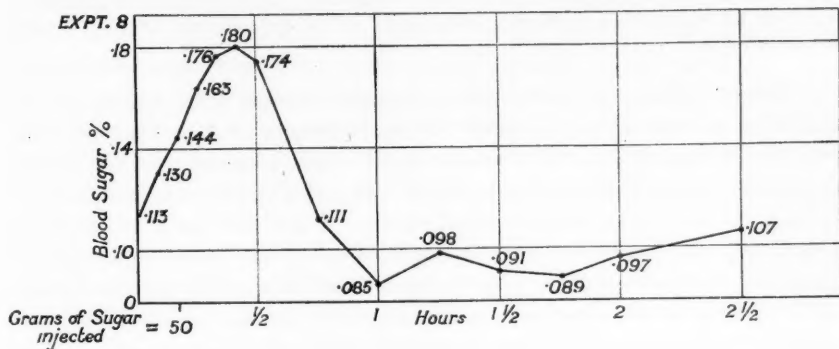
Table III shows the results of these four experiments.

TABLE III.

	Hours.									
	0	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{3}{4}$	1	$1\frac{1}{4}$	$1\frac{1}{2}$	$1\frac{3}{4}$	2	$2\frac{1}{2}$
<i>Experiment 4.</i>										
Dose: 50 grm. in 100 c.c.										
Subject W. W. P.										
Blood-sugar %	0.114	0.102	0.175	0.159	0.141	0.145	0.117	—	0.114	0.111
Stomach-sugar %	—	39.2	29.8	27.5	19.8	11.4	7.4	—	2.7	—
„ free HCl	—	tr.	tr.	nil	nil	tr.	+	—	+	—
<i>Experiment 5.</i>										
Dose: the same.										
Subject R. H.-W.										
Blood-sugar %	0.115	0.127	0.166	0.175	0.155	—	0.125	—	0.084	0.100
Stomach-sugar %	—	7.2	6.2	2.7	1.1	—	nil	—	nil	—
„ free HCl	—	nil		(much mucus present in all samples)						
<i>Experiment 6.</i>										
Dose: 50 grm. in 500 c.c.										
Subject W. W. P.										
Blood-sugar %	0.112	0.137	0.157	0.151	0.132	0.144	0.108	—	0.092	0.100
Stomach-sugar %	—	10.4	8.7	7.3	6.6	4.7	1.7	—	0.5	—
„ free HCl	—	+	++	++	++	++	++	—	++	—
<i>Experiment 7.</i>										
Dose: the same.										
Subject R. H.-W.										
Blood-sugar %	0.122	0.144	0.178	0.164	0.138	0.125	0.113	0.104	0.090	0.099
Stomach-sugar %	—	6.0	8.5	7.2	6.3	3.5	2.3	0.3	nil	—
„ free HCl	—	tr.	++	++	++	++	++	++	+	—

These figures do not yield much information, but the following points are worth noting: Firstly, in every curve the descent has begun while there is still a fair quantity of sugar in the stomach. Secondly, the curves resulting from experiments 4 and 5 show a secondary rise, which is also seen in several of the curves from the other normal subjects (see Tables I and II). There is sufficient sugar remaining in the stomach at this time for these rises to be caused by a sudden gush into the duodenum. Thirdly, the stomach still contains some sugar when the blood-sugar has returned to normal.

Experiments 8, 9, and 10. Subject 2 (R. H.-W.). In these experiments glucose was injected straight into the duodenum by means of an Einhorn's duodenal tube. In *experiment 8*, 50 grm. of glucose in 500 c.c. of water were injected as fast as possible without causing discomfort. The injection took 11 minutes. Samples of blood were taken every 5 minutes for the first $\frac{1}{2}$ hour; and thereafter every $\frac{1}{4}$ hour till $2\frac{1}{2}$ hours. In *experiment 9* a similar solution was put in slowly, at the rate of 5 c.c. a minute, thus taking 100 minutes to complete the injection. Samples of blood were taken every 5 minutes for 1 hour, and every 10 minutes for the next 100 minutes. In *experiment 10* a 6 per cent. solution was injected at the rate of 20 c.c. a minute. As at the end of 1 hour this began to cause discomfort, the rate of injection was reduced to 18 c.c. a minute for the next $\frac{1}{4}$ hour, and subsequently to 12 c.c. a minute for another



$\frac{1}{4}$ hour, when the injection had to be discontinued. In all, 99 gm. of glucose in 1650 c.c. of water were injected. Samples of blood were taken every 5 minutes for two hours.

Taken together, the most striking features of these three curves are the similarity of their ascending limbs and the difference in their form after the peak has been reached. It is of interest to note that, when dextrose is given by the mouth, the rate of rise in 70 per cent. of both pathological and normal subjects is the same as in these three duodenal curves. This is not easily explained, as a decidedly more rapid rise would be expected when the dextrose was injected direct into the duodenum, especially in experiment 8, in which 50 gm. were given in 11 minutes: in this experiment, at the end of 20 minutes, the blood-sugar had reached 0.174 per cent., while experiment 9 gives the same reading at 20 minutes when only 10 gm. of glucose had been given. These observations suggest that, unless the stomach empties unusually slowly, the rate of emptying does not have much effect on the ascending limb of a curve. (After the first 20 minutes experiment 10 cannot be considered with the others, as more glucose was injected and the bulk of the fluid was so great as to cause discomfort.)

After the first 20 minutes there is a marked variation in the other two curves, but only in so far as the time when the descents begin, for the two descents are almost identical when once they have started. In experiment 8 the descent begins 14 minutes after the injection is complete, and by 45 minutes the blood-sugar is normal. In experiment 9 the descent is delayed till 90 minutes, and at 111 minutes the blood-sugar is normal. Two points emerge from these findings: firstly, that the body can deal with 50 gm. of glucose in 45 minutes, and secondly that a continuous delivery of glucose, even though it is small, will prevent the fall in the blood-sugar. The rate of fall in these two curves, when once it has begun, is rapid and corresponds with the rate of fall found by Jørgensen and Plum (15) after intravenous injection of glucose, but in none of our curves, obtained when the glucose was given by mouth, is there a fall of such steepness. As the rate of fall in experiment 8 was the same as that following intravenous injection, it would be reasonable to assume that the whole of the sugar had been absorbed in 25 minutes. If this is so, the rate of absorption from the intestine is of little consequence.

The conclusion we would draw from these experiments is that, while the rate of emptying the stomach has but little effect on the ascending limb of a curve, it has considerable control over the time and rate of a fall.

C. *Nausea*. As has been pointed out by H. J. John (11), sensations of nausea may have some effect on a blood-sugar curve. This is shown in two ways. Firstly, when nausea follows the drinking of the sugar, the usual rise at the end of the first $\frac{1}{4}$ hour is absent (as in curves 1, 11, and 12). This is almost undoubtedly due to the failure of the stomach to begin emptying (cf. Ryle (12)). Secondly, when nausea occurs during the test, there is often a dip in the curve. This is well shown in experiment 10, when each attack of nausea is followed by a fall in the blood-sugar. The two dips in this curve are, presumably, due to

the cessation of intestinal peristaltic movements and consequent slowing of the rate of absorption. The drop in curve 6 also synchronizes with an attack of nausea which lasted from $\frac{1}{2}$ to 1 hour after the glucose had been taken.

D. *Age.* While several writers have referred to the possible effects of age on sugar tolerance, only Spence (13) and Punschel (14) appear to have made any attempt to examine the question experimentally, and, unfortunately, both these writers took as their subjects, not healthy people, but patients undergoing treatment.

Study of Tables I and II, and of the curves in the Appendix, shows that there are considerable differences in the response to a dose of dextrose in the more elderly subjects as compared with young persons. The difference in the fasting value is very slight, but the height of the peak and the time taken for the blood-sugar to return to normal are both definitely increased. The highest peak obtained from the 11 healthy young subjects was 0.203 per cent. This figure was exceeded in 5 of the 14 curves obtained from elderly subjects. In the series of young subjects only one curve failed to return to normal (0.120 per cent.) in 2 hours, while 10 out of the 14 curves from the elderly subjects failed to do so.

The Range in Health.

From the above considerations we submit that, as the mental state of the individual, the rate of emptying the stomach, nausea, and lastly age, may some or all play their part in the form of any particular blood-sugar curve, it is impossible to describe a curve normal for all healthy subjects. Consequently it is not surprising that the figures in Tables I and II show wide variations. Nevertheless, there are certain salient features to which limits can be assigned and within which limits a curve should fall to be consistent with health. These are:

1. The fasting blood-sugar level.
2. The maximum blood-sugar obtained.
3. The time taken for the blood-sugar to return to normal.

The fasting blood-sugar level. Gray (4), in a review of 431 tolerance tests on apparently healthy people, finds that in the majority the fasting blood-sugar level lies between 0.08 per cent. and 0.12 per cent. Only a few exceeded 0.12 per cent. Our own findings are in substantial agreement with this. Tables I and II show that age has but little effect on the level of the fasting blood-sugar.

The maximum blood-sugar obtained. Here the question of technique must be considered, for after the injection of glucose the sugar-content of venous blood is less than that of capillary blood. The conclusions drawn here are, therefore, not applicable to work in which venous blood is used. The frequency of taking samples of blood is also of importance in this connexion, for the greater the number of samples, the more nearly will the peak of the curve represent the maximum blood-sugar.

In Table I the highest reading among the young subjects is 0.203 per cent.,

and there are 5 curves having readings over 0.180 per cent. Other authors (e. g. Höst (8) and Hagedorn (3)) have frequently found readings above 0.180 per cent. in young subjects. For these reasons MacLean and de Wesselow's suggested maximum of 0.180 per cent. seems too stringent a limit. A maximum of 0.20 per cent. is more reasonable.

The effect of age on the peak is shown in Table II. There are 10 subjects aged over 70, and 5 of these gave curves with a peak above 0.210 per cent., viz.: curves from subjects aged 71, 72, 76, 78, and 98 had peaks of 0.212, 0.220, 0.224, 0.240, and 0.310 per cent. respectively.

From subjects between the ages of 50 and 70 there are 4 curves in Table II, and we have only been able to find 2 others (Hagedorn) obtained under comparable conditions. None of our 4 curves has a high peak, but Hagedorn's 2 subjects (aged 50 and 62) had peaks of 0.214 per cent. and 0.205 per cent. Therefore, though it is impossible to say, from the data available, at what age the change begins, it is clear that in old age the peak tends to be higher, and that many apparently high curves from elderly subjects are in reality within the normal range when the age is taken into consideration. The material presented in this paper is insufficient for the formation of any scale by which the height of the peak may be judged as age increases, but as a basis for discussion it is suggested that a peak of 0.220 per cent. at the age of 70, rising to 0.240 per cent. at 80, may be considered normal. Between the ages of 50 and 70 we have hardly any data, but it would appear that a peak of 0.210 per cent. at 60 should not be considered abnormal.

The time taken for the blood-sugar to return to normal. Here again the question of technique has to be considered, for, as has been shown by Hagedorn (3), the blood-sugar returns to normal in the venous blood earlier than in the capillary blood. For the sake of convenience the normal blood-sugar has been taken as 0.120 per cent., i. e. the upper limit of the fasting blood-sugar. In our series of 11 healthy young subjects only 1 failed to return to normal in 2 hours, but at $1\frac{1}{2}$ hours 8 had failed to return to normal. It will be seen that these observations differ somewhat from MacLean and de Wesselow's dictum that a normal curve should return to normal in $1\frac{1}{2}$ hours.

In Table II only 4 out of the 14 curves from elderly subjects have returned to 0.120 per cent. in 2 hours, but all have fallen below 0.120 per cent. at 3 hours with the exception of 3 in which the test was stopped at $2\frac{1}{2}$ hours, and in these 3 curves the fall was so rapid as to make it seem likely that the readings at 3 hours would have been 0.120 per cent. or less.

It is evident that, in considering the return to normal, so rigid a time limit as $1\frac{1}{2}$ hours cannot be maintained even in young adults. It is suggested that this period be extended to 2 hours in those under 30 years, and to 3 hours in those over 60. There is no evidence on which to base any conclusions for the intervening 30 years.

Conclusions.

1. The dextrose tolerance test should be made on a fasting, resting subject. The dose should be 50 grm. Capillary blood should be used by pricking the finger-tip.
2. The normal fasting value lies below 0.12 per cent. at all ages.
3. The upper limit for the rise of the blood-sugar in young adults is 0.20 per cent.
4. Taking 0.12 per cent. as the normal, the blood-sugar should return to this level in 2 hours in young adults.
5. Certain changes take place in sugar tolerance curves in old age, viz. a higher rise and a slower fall.
6. The upper limit for the rise at the age of 70 is 0.22 per cent. increasing to 0.240 at 80.
7. The time taken for the blood-sugar to return to normal should be within 3 hours for those over 60 years of age.
8. The rate of emptying the stomach does not appreciably affect the ascending limb of a curve.
9. A delay in the emptying of the stomach may cause a considerable delay in the return of the blood-sugar to the normal level.
10. Nausea during the test causes a fall in the blood-sugar.

Our thanks are due to Dr. J. H. Ryffel for permission to use his laboratory, and to the authorities of Lambeth for their hospitality and co-operation, and also to all the subjects, who placed one or more mornings at our disposal and who endured the discomforts of coming to the hospital breakfastless.

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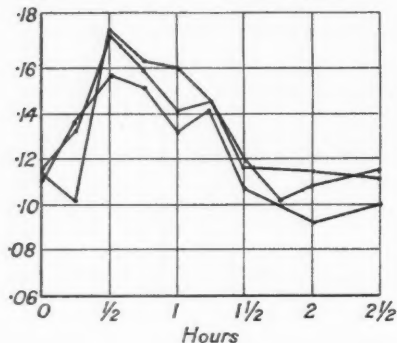
APPENDIX.

SUGAR TOLERANCE CURVES FROM TABLE I.

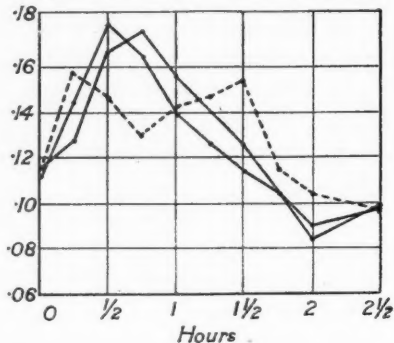
(Healthy male adults under 30 years.)

*Dose: 50 gm. of dextrose in 100 c.c. of water.**Continuous line indicates that the subject walked about during the test.**Broken line indicates that the subject was kept sitting during the test.**In all cases the broken line represents the last curve obtained from a subject.*

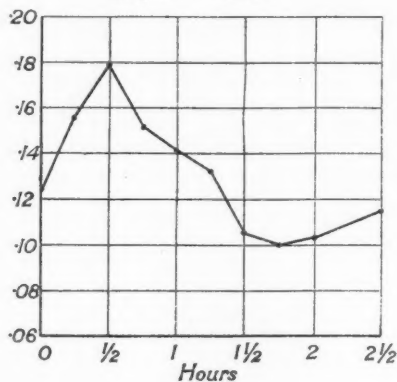
Subject 1 (W. W. P.) Curves 1, 2, and 3.



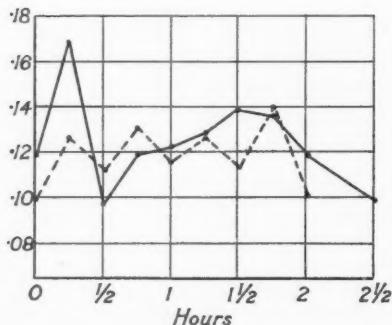
Subject 2 (R. H.-W.) Curves 4, 5, and 6.



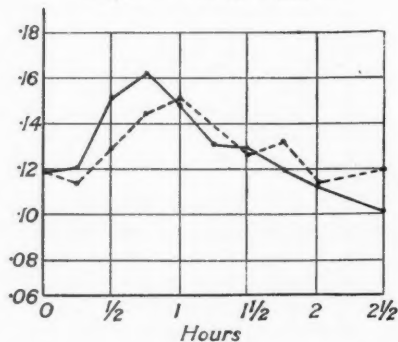
Subject 3. Curve 7.



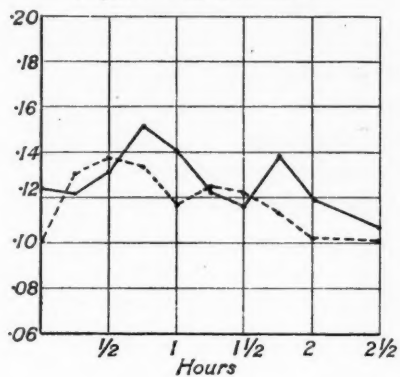
Subject 4. Curves 8 and 9.



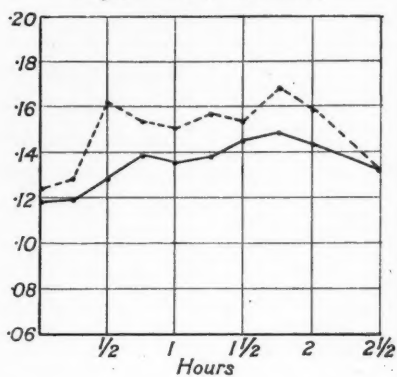
Subject 5. Curves 10 and 11.



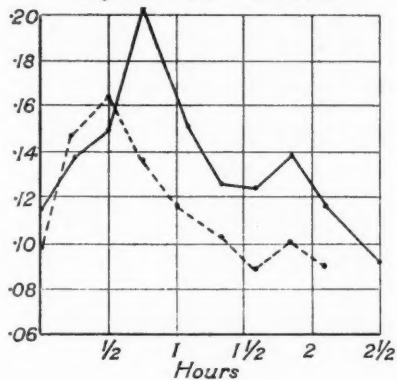
Subject 6. Curves 12 and 13.



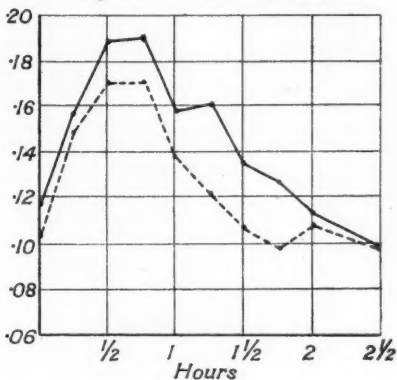
Subject 7. Curves 14 and 15.



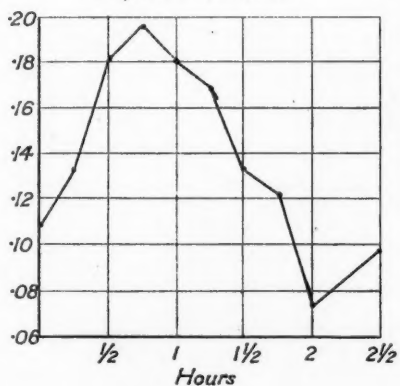
Subject 8. Curves 16 and 17.



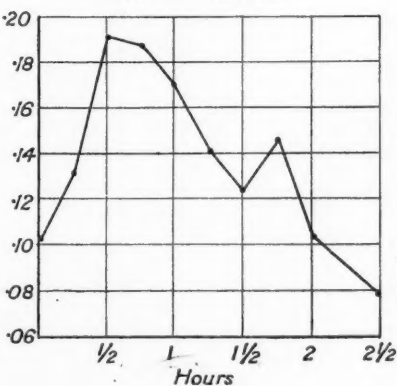
Subject 9. Curves 18 and 19.



Subject 10. Curve 20.



Subject 11. Curve 21.



SUGAR TOLERANCE CURVES FROM TABLE II.

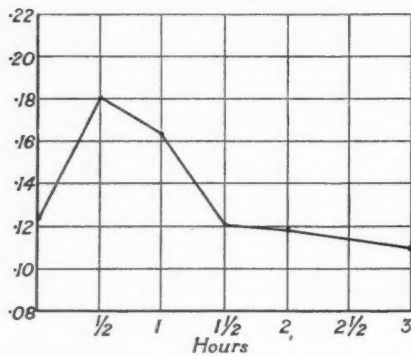
(Healthy subjects over 60 years.)

Curves arranged in order according to age.

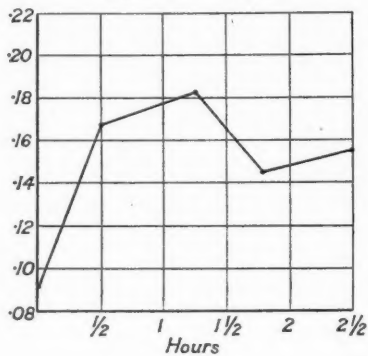
All these subjects were kept in bed on the morning of the test.

Dose: 50 gm. of dextrose in 100 c.c. of water.

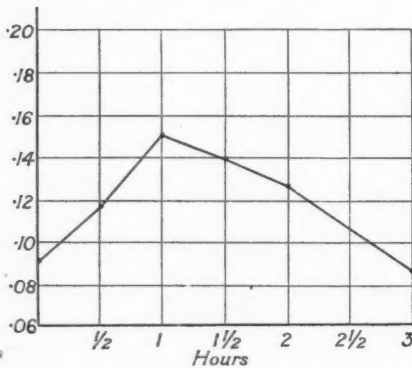
Subject 12. Curve 22.



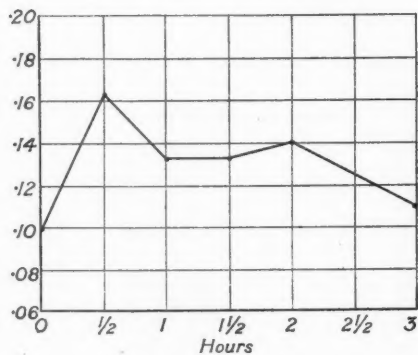
Subject 13. Curve 23.



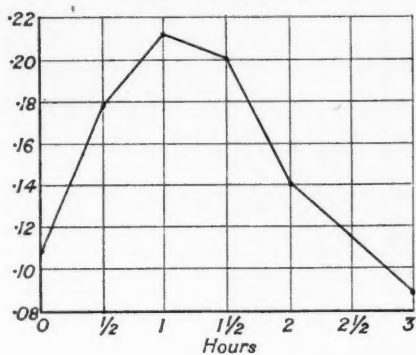
Subject 14. Curve 24.



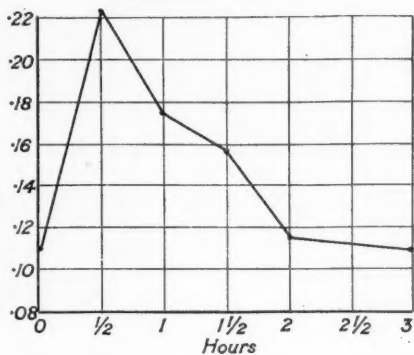
Subject 15. Curve 25.



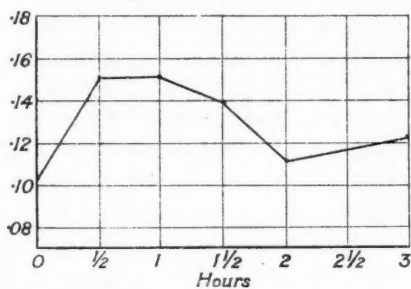
Subject 16. Curve 26.



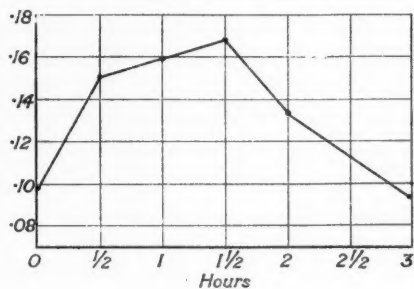
Subject 17. Curve 27.



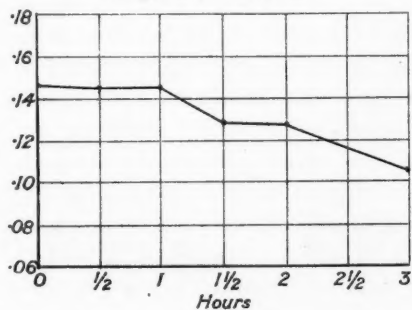
Subject 18. Curve 28.



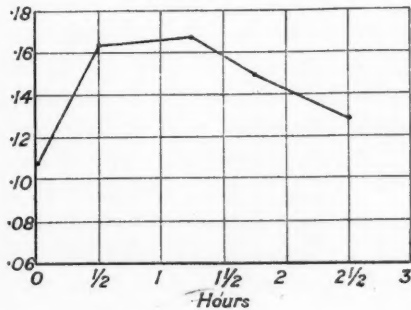
Subject 19. Curve 29.



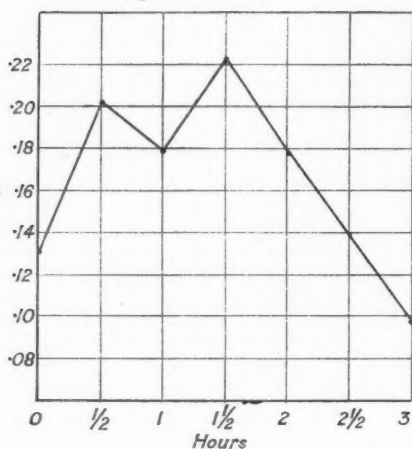
Subject 20. Curve 30.



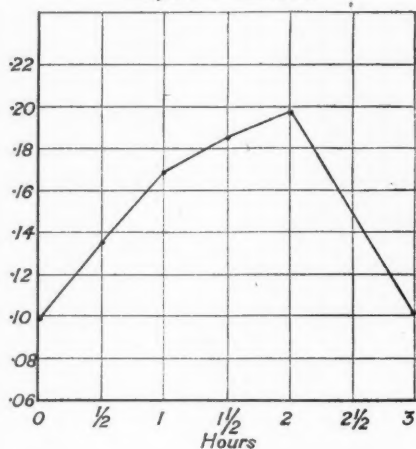
Subject 21. Curve 31.



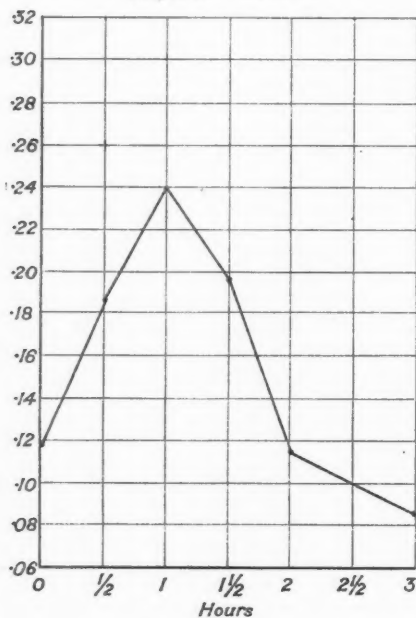
Subject 22. Curve 32.



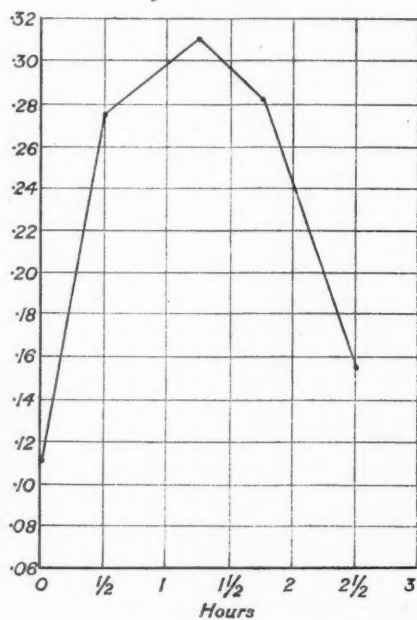
Subject 23. Curve 33.



Subject 24. Curve 34.



Subject 25. Curve 35.



THE EFFECT ON RENAL EFFICIENCY OF LOWERING THE BLOOD-PRESSURE IN CASES OF HIGH BLOOD-PRESSURE¹

By CHARLES REID

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THE following investigation was undertaken to ascertain the effects, especially as regards the efficiency of the kidneys, of lowering the hypertension present in cases which did and others that did not show evidence of renal disease. The plan adopted was to make the following examinations on each case before, during, and after periods of administration of vasodilator drugs; the amounts of urea and non-protein nitrogen in the blood, the power of the kidney to concentrate urea after a dose of 15 grm. urea (MacLean's test (9)), the total amount of urea and the total volume of urine excreted, records of blood-pressure, pulse, respiration, and general condition of the subject being made also.

A current conception of elevated blood-pressure is that, while attended by drawbacks in the way of increased heart work and stress on the arterial walls, it is in large measure a compensatory process in the organism. This view has gained wide acceptance, and many observers have emphasized the inadvisability of indiscriminate lowering of the pressure by such artificial means as the use of vasodilating drugs. Cases have been cited of deterioration in general condition being associated with lowering of high pressures, and, on the other hand, improvement in health being attended, not by lowering, but by some further rise of an already elevated pressure. The high-pressure levels in such cases are regarded as not being excessive in the circumstances, but rather as optimal, or at least not markedly superoptimal under the conditions present in the body at the time. When no symptoms are in evidence artificial reduction of the pressure is held to be inadmissible. Even when symptoms are present it is conceivable that a necessary compensatory action may be exercised in some respects, though the high pressure may involve disturbances in other respects.

In view of the separation of a new antipressor principle from hepatic extracts in comparative purity by James, Laughton, and Macallum (7), and of the prospect of this method of lowering the raised blood-pressure being given

¹ Received December 10, 1925.

an extended clinical trial, the importance of data dealing with the efficiency of the kidney under conditions of lowered blood-pressure is obvious—with regard to the differentiation of cases in which reduction of high pressure may be permissible or desirable or the reverse. Some results of the clinical use of the hepatic extracts have been described by Macdonald (8), by Major (13), and by Major and Stephenson (15). Major (14) reported that in two cases of hypertension the excretion of guanidine was not diminished, but rather increased, during a period (several days) of blood-pressure lowering by hepatic extracts. Gruber, Shackelford, and Ecklund (4) found that, when high arterial pressure was lowered by pheno-barbital, no harmful effect was produced on the excretion of phenolsulphonephthalein.

The latter, however, is a foreign substance, and might be thrown out by the kidney independently of any but very extensive changes in blood-pressure, so that, while the above investigation agrees, so far as phenolsulphonephthalein is concerned, with the findings of the present investigation as regards urea, the evidence obtained in the former inquiry is not necessarily valid as an argument against the compensatory theory.

Possible Compensatory Mechanisms.

It is evident that elevated blood-pressure might be a compensatory adjustment in the way of driving more blood through some vital organ, e.g. brain, heart-muscle, or kidney: such might be needed where there is inadequacy of blood-flow depending on alteration in its vascular channels, arterial or capillary, or when, even apart from such alteration, a higher capillary pressure and more rapid blood-flow would be beneficial in enhancing the functioning of an organ—deficient from structural or other causes.

There is the familiar instance of the mechanism by which an interference with the normal blood-supply to the head (e.g. cerebral compression, experimental closure of the carotids) promptly calls forth a rise of aortic pressure with an obviously compensatory significance through excitation of the vasomotor centre, causing constriction in the splanchnic and other areas, and diminution of the activity of the vagus centre leading to increased action of the cardiac pump. The recent experimental work of Anrep and Starling (1) by cross-circulation experiments shows the converse action of increased blood-pressure in the head in depressing the vasomotor centre, in addition to the well-known influence of such pressure in stimulating the vagus centre and slowing the heart.

L. Hill (6) wrote in 1900, 'The vasomotor centre is not only excited reflexly, but responds to every change in the circulation through the spinal bulb. A rise of pressure in the cerebral arteries provokes a fall of aortic tension; conversely, a fall of pressure in the cerebral arteries provokes a rise. In other words, cerebral anaemia, however produced, excites the centre and increases vascular tone, while cerebral hyperaemia decreases vascular tone.'

In cases of high blood-pressure Starling (17) attaches much importance

to a stimulating influence on the vasomotor centre resulting from a defective blood-supply to that centre. The remarkable variability of the pressure from day to day or hour to hour in some high-pressure cases has to be kept in mind in relation to such a view.

It is obviously possible that with regard to other vital organs, as in the case of the brain, there may be vascular adjustments of a compensatory character involving a rise of aortic pressure.

In the case of the kidney a rise of general blood-pressure might have a compensatory value in aiding the excretion of concentrated urine, salts, abnormal substances, or excess of acid or other waste products; or, again, when the materials to be excreted are not abnormal or excessive in amount, but the functioning of the organ is defective from structural change or other causes. The improvement might be associated with increase in the flow of water or determined in other ways.

Bier (2) first suggested that hypertension with the arteriosclerotic or atherosclerotic kidney is best regarded as a compensatory effort of the organism, to be interfered with only when danger threatens either of cardiac failure or of cerebral haemorrhage. According to this view, by diminishing hypertension, a danger more or less imminent would be replaced by the certain danger derived from an upset of the kidney efficiency, maintained only at an efficient level by the raised blood-pressure.

Relations of Blood-pressures and Renal Efficiency.

The existing data bearing on the frequent coexistence of high blood-pressures and defective kidney efficiency do not afford grounds for determining the relations between the former and the latter. Examination of the relations between the heights of the blood-pressures and the existence and degree of ascertained defects in urinary excretion (urea, &c.) as studied in different individuals is obviously inadequate, since the degree of kidney damage which may be present in the different subjects constitutes a factor of unknown value. This factor may obviously determine various relations between the levels of blood-pressures present and the degrees of defect in urinary excretion. If it is assumed for the moment that high blood-pressure (as many believe) can favour kidney efficiency, the fact remains that there might be very different degrees of defective excretion in presence of equally high blood-pressures, and, on the other hand, that excretion might be relatively good in association with comparatively low blood-pressures—the existence of varying (unknown) amounts of kidney damage constituting the deciding factor in the different subjects examined.

To test the relationship of high blood-pressures and renal efficiency it is clearly necessary to make observations on the same individual in whom, with given kidney conditions, lowering of the blood-pressure is purposely induced in order to ascertain what alteration, if any, in renal efficiency occurs in association with the alteration in the blood-pressure, the response of the kidneys

to a definite test (urea concentration) being ascertained, while the blood urea and the non-protein nitrogen are also examined.

As regards the known relation of blood-pressure to the excretion of water, Herringham (5) states that, broadly speaking, blood-pressure and amount of urine vary together, though not from day to day in individual cases; in disease the quantity of urinary water does not vary so directly with blood-pressure as might be expected. The urine may diminish while the pressure is steady, or the urine may remain steady while the pressure falls. Such variations are not accounted for by fresh access of local inflammation in the kidney, &c.; they are ascribed to local vascular changes.

Deviations from the general relationship between height of general blood-pressure and volume of urine are readily intelligible in view of what is known of the occurrence of special alterations in the calibre of the renal vessels from nervous or chemical influences, apart from or in addition to variations in aortic pressure, as well as the effects of changes in the composition of the blood (hydraemia, presence of diuretic constituents, &c.), such being capable of affecting the water excretion without parallel change in aortic pressure. But in view of the general relationship between blood-pressure and urinary volume it is, of course, to be expected that the administration of nitrites should have decided effects.

Mason (16) has recently found that sodium nitrite alters the urinary volume sufficiently and frequently enough to warrant its withdrawal during a water test for renal efficiency; the effects on blood and urinary nitrogen were not described.

There is no evidence of nitrites influencing kidney function otherwise than through the vascular changes induced. It is evident that dilatation of the renal vessels and the usual fall of general blood-pressure under nitrites act in different directions on the flow of urine, the former tending to give increased transudation or filtration, and the latter to diminish the excretion of water. Upon the relative predominance of one or other of these two influences the urinary result will naturally depend.

The Method employed in the Study of the Renal Efficiency of Cases with High Blood-pressure and of the same Cases under the Influence of Vasodilators.

On the first day of examination, breakfast was taken about 5 a.m. No food or drink was allowed after this until after completion of the urea concentration test on that day.

About 9.30 a.m. to 10 a.m. at least 6 c.c. of blood were removed by puncture of one of the veins over the anterior aspect of the elbow, and received into a sterile test-tube containing a small quantity of powdered neutral potassium oxalate. The blood was used for the estimation of the urea and non-protein nitrogen.

Immediately after the vein puncture, the bladder was emptied, and 15 grm. of urea in 100 c.c. of water administered.

Specimens of urine were obtained, with the exception of one or two cases, at

one hour, two hours, three hours after the administration of the 15 gm. urea. The quantity, urea concentration, specific gravity, presence of albumin, examination of the centrifugalized deposit, were noted. The patient was then allowed to resume his normal diet, and in the course of the afternoon, between 2 p.m. and 3 p.m., the exhibition of liquor trinitrini Oij three-hourly for the succeeding twenty-four hours was commenced.

In one series of cases referred to in Table VI, erythrol tetranitrate was used as a vasodilator; the general effects are seen to be similar. On the second day of examination, i. e. about eighteen hours after the administration of the first dose of trinitrinum, the same examinations of the blood and urine were carried out at approximately the same time and with the same routine.

After the completion of the second urea test no further trinitrinum was given. On the third day, the blood and urine were examined again as before.

Blood-pressure readings, both systolic and diastolic, pulse-rates, and respiration-rates were observed each day during the forenoon in practically every case. Full clinical notes were also made. No difficulty was experienced in getting blood from the same vein on successive days, so that the other arm was always used for blood-pressure readings.

In Case 1 no liquor trinitrini was employed, as a venesection was decided on by the medical officer in charge of the case. No untoward effects due to the liquor trinitrini were observed except in one or two cases. One case (No. 2) complained of flushes and palpitation, while another case (No. 7) did not show a lowered blood-pressure until the liquor trinitrini had been administered in two-minim doses three-hourly for forty-eight hours, and three-minim doses four-hourly for the succeeding twenty-four hours. This caused the patient to vomit and to suffer from headache, palpitation, &c., while his blood-pressure fell considerably on the third day of the administration of the liquor trinitrini.

One or two cases showed a slight increase in the urea and non-protein nitrogen of the blood while under the influence of the vasodilator. In order to make certain that this increase in the blood urea was not due to diminished power of the kidney, while the blood-pressure was lowered, to excrete the increased amount in the blood due to the giving of the initial dose of urea on the preceding day, the above routine was slightly altered as follows in a series of cases:

1st day: Routine examination of blood, urine, &c.

2nd day: Administration of the trinitrinum begun.

3rd day: Routine examination of blood, urine, &c. Trinitrinum stopped after completion of the urea concentration test.

4th day: Nil.

5th day: Routine examination of blood, urine, &c.

In all cases patients were kept in bed throughout the three- or five-day periods of examination to obviate as far as possible the influence of variations in external temperature, &c., on diuresis.

TABLE I.

Date.	Sex and Age.	Blood-pressure.		Pulse-pressure.	Syst. B-P. Fall.	Pulse-rate.	Resp.	Blood Urea.	Non-pro. Nit.	Urea Concentration.			Quantity in c.c.			Total.	Amt. Urea in grm.			Total.
		Syst.	Diast.							1st Hr.	2nd Hr.	3rd Hr.	1st Hr.	2nd Hr.	3rd Hr.		1st Hr.	2nd Hr.	3rd Hr.	
(1)																				
14.8.24	M. 53	220	120-30	90-100	—	100	20	47	42	1.3	1.7	2.1	235	165	145	545	3.1	2.9	3.0	9.0
15.8.24		160	100	60	60	90	18	43	31	2.3	2.8	3.1	140	125	50	315	3.2	3.5	1.5	8.2
16.8.24		210	132	78	—	98	20	52	42	1.7	2.0	2.4	110	150	135	395	1.9	3.1	3.3	8.3
(2)																				
15.8.24	F. 70	216	110	106	—	68	18	36	—	1.4	2.2	—	190	170	—	360	2.7	3.3	—	6.0
16.8.24		184	90	94	32	72	20	34	22	1.8	3.0	—	210	90	—	300	3.7	2.7	—	6.4
17.8.24		184-6	94-8	90	30	76	20	32	21	1.5	2.3	—	180	125	—	305	2.7	2.9	—	5.6
18.8.24		204	100	104	—	70	18	32	—	1.2	2.3	—	190	—	—	—	2.5	—	—	—
(3)																				
18.8.24	M. 72	180	72	108	—	58	—	28	34	2.1	2.9	3.7	150	105	55	310	3.2	3.0	2.1	8.3
20.8.24		144	60	84	36	64	—	25	31	3.1	3.7	3.4	95	60	55	210	2.9	2.2	1.9	7.0
21.8.24		164	70	94	—	60	—	25	31	2.5	3.0	3.3	130	80	55	265	3.3	2.4	1.9	7.6
(4)																				
18.8.24	M. 75	204	106	100	—	58	30	73	43	1.6	2.0	2.3	250	70	40	360	4.0	1.4	0.9	6.3
20.8.24		190	100	90	14	62	30	110*	77*	3.7	3.5	3.5	110	55	55	220	4.1	1.9	1.9	7.9
21.8.24		—	—	—	—	—	—	77	53	3.8	3.7	3.8	145	60	66	271	5.5	2.2	2.5	10.2
(5)																				
22.8.24	M. 72	184	70-6	110	—	58	18	64	39	1.8	2.0	2.4	205	195	65	465	3.7	4.0	1.6	9.3
23.8.24		160	56-60	100	24	62	20	68	41	2.4	2.7	2.8	180	80	45	305	4.3	2.2	1.8	7.8
24.8.24		180	68-70	110	—	55	18	67	40	4+	4+	4+	230	85	85	400	—	—	—	16+
10.9.24		—	—	—	—	—	—	—	—	1.6	1.4	1.3	224	222	94	540	3.6	3.1	1.7	8.4

* Urea given shortly before vein puncture.

Remarks.—(1) Chr. nephritis and dilatation of heart. Venesection 37 oz. 14.8.24 : Urine alb. tr. R. B. C.'s : gran. casts.
 (2) Hemiplegia (R.) duration 4/12 yrs. Urine alb. tr. R. B. C.'s : + occasional gran. casts.
 (3) Arteriosclerosis. Urine nil.
 (4) Arteries very sclerosed. Urine nil.
 (5) Arteriosclerosis : loss of memory. Urine nil.

(6)	22.8.24	M. 78	170	105	65	—	80	20	94	61	26	27	3.1	50	55	40	145	1.3	1.5	1.2	4.0
	23.8.24		150	90-5	55-60	20	73	18	89	59	2.7	3.1	3.3	80	40	45	165	2.2	1.2	1.5	4.9
	24.8.24		164	100	64	—	78	20	89	59	2.7	2.9	3.1	60	70	55	185	1.6	2.0	1.7	5.3
(7)	22.8.24	M. 57	220	125	95	—	76	16	133	66	1.1	1.2	1.4	235	50	100	385	2.6	0.6	1.4	4.6
	23.8.24		—	—	—	—	—	—	138	77	—	—	—	—	—	—	—	—	—	—	—
	24.8.24		230-40	125-30	110	—	—	—	130	67	1.5	1.6	1.7	235	140	130	525	3.9	2.2	2.2	8.3
	26.8.24		170	110	60	50	93	20	153	82	2.1	2.2	2.3	300	25	35	360	6.3	0.5	0.8	7.6
	28.8.24		216	105	110	—	72	16	150-70	78	1.8	1.8	1.8	160	115	30	305	2.9	2.0	0.5	5.4
(8)	25.8.24	M. 58	142	56	86	—	102	C.S.*	138	92	3.1	3.3	3.3	185	75	65	275	4.2	2.5	2.1	8.8
	26.8.24		130	64-6	65	12	92	33	177	102	3.1	3.1	3.1	140	70	60	270	4.3	2.1	1.9	8.3
	27.8.24		144	60-2	80	—	85-90	C.S.*	210	98	3.0	2.9	—	220	70	—	—	6.6	2.0	—	—
(9)	25.8.24	M. 54	184	96-8	88	—	63	20	63	48	1.5	2.2	1.8	180	80	85	345	2.7	1.8	1.5	6.0
	26.8.24		150-2	90-2	60	30	62	22	59	52	1.7	2.7	2.4	210	85	40	335	3.6	2.3	1.0	6.9
	27.8.24		170-4	94-6	80	—	54	18	60	46	1.6	2.0	1.9	245	105	115	465	3.8	2.1	2.2	8.1
(10)	25.8.24	M. 81	240	125	115	—	60	—	68	55	1.1	1.5	1.8	300	160	100	560	3.3	2.4	1.8	7.5
	26.8.24		172-6	110-2	60	68	63	—	68	56	2.7	3.8	4.0	115	50	40	205	3.1	1.9	1.6	6.6
	27.8.24		220-5	120-5	100	—	60	—	60	53	2.1	2.3	2.4	130	155	130	415	2.8	3.7	3.1	9.6
(11)	29.8.24	M. 26	160-2	105-10	55	—	70	12	44	38	1.7	1.5	1.9	90	155	105	350	1.5	2.4	2.0	5.9
	31.8.24		130	90	40	30	75	17	40	38	1.2	1.6	2.1	245	150	115	510	3.1	4.1	2.4	9.6
	2.9.24		136	80-5	50	—	75	13	40	42	2.0	2.1	2.6	135	95	62	292	2.7	2.0	1.6	6.3

* C.-S. = Cheyne-Stokes.

Remarks.—(6) Arteriosclerosis: arthritis deformans. Urine nil.

(7) Chr. nephritis: rheumatoid arthritis. Lead poisoning (25 yrs. ago). Urine alb. tr.: occasional R. B. C.'s. Sickness, vomiting, &c., during night of 25/26.8.24.

(8) Myocarditis. Urine clear. Died 27.8.24.

(9) Arteriosclerosis with Stokes-Adams' syndrome (?). Urine clear.

(10) Myocarditis with rheumatoid arthritis. Urine clear.

(11) Acute nephritis (5 days). Urine alb. +. Blood cells and casts present.

TABLE I (continued).

Date.	Sex and Age.	Blood-pressure.		Pulse- pres- sure.	Syst. B.-P. Fall.	Pulse- rate.	Resp.	Blood Urea.	Non- pro. Nit.	Urea Concentration.			Quantity in c.c.			Total.	Amt. Urea in grm.			Total.
		Syst.	Diast.							1st Hr.	2nd Hr.	3rd Hr.	1st Hr.	2nd Hr.	3rd Hr.		1st Hr.	2nd Hr.	3rd Hr.	
(12) 29.8.24 31.8.24 2.9.24	M. 21	150 130 150-4	75-80 70 75-85	75 60 70	— 20 —	70 70 63	18 16 15	41 40 43	35 35 38	1-6 2-0 2-0	2-1 2-8 2-7	2-3 2-9 2-9	150 225 237	75 65 47	85 65 43	310 355 327	2-3 4-6 4-6	1-6 1-8 1-3	2-0 1-9 1-3	5-9 8-3 7-2
(13) 30.8.24 1.9.24 3.9.24	F. 60	280-90 230-50 275-300	150-5 130-40 130-45	130 100 130	— 50 —	94 86 83	26 24 20	58 — —	43 — —	1-4 2-4 2-6	2-1 2-7 2-6	2-5 2-9 3-0	120 125 81	150 82 90	100 62 70	370 269 241	1-7 3-0 2-1	3-1 2-2 2-4	2-5 1-8 2-1	7-3 7-0 6-6
(14) 29.8.24 31.8.24 2.9.24	F. 40	130 114-20 130	75 80 80-5	55 40 50	— 15 —	83 90 84	20 20 19	48 46 45	38 38 42	2-9 1-9 1-9	4-0 2-7 2-4	4-2 3-5 3-1	125 210 200	75 80 95	60 75 65	260 365 360	3-7 4-1 3-8	3-0 2-2 2-3	2-5 2-7 2-0	9-2 9-0 8-1
(15) 30.8.24 1.9.24 3.9.24	F. 63	194-204 170 190+	90 80-5 80-5	110 90 110	— 30 —	65 64 54	16 16 14	49 49 49	39 39 41	2-1 2-0 1-9	2-7 2-7 2-7	2-6 2-9 2-8	90 86 90	60 75 67	50 40 40	200 201 197	1-9 1-7 1-7	1-6 2-0 1-8	1-3 1-2 1-1	4-8 4-9 4-6
(16) 30.8.24 1.9.24 3.9.24	M. 71	180 155 176	80 80 80-5	100 75 90	— 25 —	65 80 72	16 18 16	41 42 39	38 41 38	2-3 2-1 2-2	2-4 2-5 2-8	2-4 3-0 2-7	170 155 135	60 87 80	95 60 45	325 302 260	3-9 3-3 3-0	1-4 2-2 2-2	2-3 1-8 1-2	7-6 7-3 6-4
(17) 4.9.24 6.9.24 8.9.24	M. 61	140 120 130	58-65 70-5 70	80 50 60	— 20 —	72 65 60	14 15 12	60 54 54	50 48 48	2-1 1-2 2-2	0-9 1-4 2-3	1-7 1-6 2-3	76 141 70	195 140 90	93 84 57	364 365 217	1-6 1-7 1-5	1-7 2-6 2-0	1-6 1-4 1-3	4-9 5-7 4-8

Remarks.—(12) Nephritis 4 months: no oedema at present. Urine alb. + : R. B. C.'s and occasional gran. casts.
 (13) Hemiplegia (R.) 5 months: very excitable. Urine alb. tr.: occasional R. B. C.'s. Blood and gran. casts.
 (14) Aneurysm of ascending aorta (with erosion of sternum). Urine clear.
 (15) Angina pectoris. Urine clear.
 (16) Arteriosclerosis: myocarditis. Urine clear.
 (17) Urine clear.

Methods: (1) *Urea.* The urease method of Van Slyke as modified by MacLean (10) was employed.

(2) *Non-protein nitrogen.* For this estimation the adaptation of Folin's method described by MacLean (11) was used.

(3) *Percentage of urea in the urine.* The hypobromite method was used, the volume of nitrogen evolved being measured within one minute after shaking, and the equivalent percentage of urea read off from tables compiled by means of estimations carried out on various specimens of urine by the urease method.

(4) *Systolic and diastolic blood-pressure.* The auscultatory method was used throughout. The patient was kept in the semi-recumbent position, and the same upper arm was employed for the compression armlet in all observations, an Oliver auditory tambour being used. The systolic blood-pressure index was always checked by simultaneous employment of the tactile method, recommended as a routine method a number of years ago by MacWilliam and Melvin (12). The diastolic pressure was taken as usual as the beginning of the fourth phase. In no cases were first readings relied on; the readings were repeated in each case several times during the course of half an hour till a constant level was obtained as shown by both auditory and tactile indices. During this time, variations in the pulse and respiration were noted. Each reading was made quickly, so as to avoid prolonged compression by the armlet, undue congestion of the arm, &c. The pressure was estimated twice in each three-hourly period, once before the middle of each period and another in its latter part. Such a distribution of the estimations tends to reduce possible disturbance of values due to any variations of pressure that may occur within the period, and give a nearer approach to the average level of pressure. Substantial lowering of pressure shows a general parallelism with the reduction in the volume of urine excreted during the same period.

The chief results obtained are stated in Table I on pp. 416-19, dealing with pathological cases of high blood-pressure, some with and others without kidney lesions, cardiovascular changes of various kinds being usually present as noted in the table. The patients were mostly in middle or advanced life—sixteen males and five females. Their general condition varied much.

The dietetic conditions were similar in almost all cases—the usual infirmary full diet. The urea test was completed and blood samples taken in the morning, no food or drink having been taken for at least five to six hours previously.

Preliminary Conclusions from the Results obtained in the Pathological Cases in Table I under the Influence of the Vasodilator Drug.

1. *Effects on the blood urea and non-protein nitrogen.* The blood urea figure and the non-protein nitrogen figure expressed in milligrams per 100 c.c. blood were not affected to any extent except in Cases 4, 7, and 8, in which a decided rise occurred. The reasons for the rise in Cases 4 and 8 are quite definite. In

Case 4 the observation was vitiated by the urea being given some minutes before the blood sample was taken, while Case 8 was a terminal one dying from aortic heart disease. In Case 7 the vasodilator drug was pushed to the point of intolerance (vomiting, &c., being induced) as the blood-pressure was affected with difficulty. This case received liquor trinitrini \mathfrak{w} ij three-hourly for two days, followed by \mathfrak{w} ij three-hourly for one day. It may be noted that in Case 8, during the period of comparatively slight lowering of systolic pressure under the influence of trinitrinum, the general condition was obviously improved, the patient much more comfortable, the pulse slower, and the Cheyne-Stokes' respiration abolished—to recur on the day following the discontinuance of the vasodilator drug when the pressure had again risen.

2. *Effect on the power of the kidney to concentrate urea.* All the cases, with one exception, showed no impairment of the power to concentrate urea. This Case—14—showed a 66 per cent. rise in the first hour in the total amount of urine excreted. With regard to the other cases, the power of the kidney to concentrate urea was increased commonly 25 per cent. up to 75 per cent. above the original value.

3. *Effect on the total quantity of the urine excreted during the three hours following the administration of 15 grm. urea.* The majority of the cases showed a decrease in the total amount of urine excreted in the three hours. The percentage decrease amounted in many cases to 20–40 per cent., with one case showing a reduction of over 50 per cent. Notable exceptions to the decrease were Cases 7, 11, and 12—the last two being recent cases of acute nephritis. Cases 11 (acute nephritis of five days' duration) and 7 showed a 40 per cent. increase in the amount of urine. The increased amount was observed principally during the first hour (Cases 11, 12, 14), and during the first and second hours (Case 7).

4. *Effect on the total urea excreted during the three hours' urea test.* The majority of the cases showed little or no substantial change. No case showed any marked cutting down of the total amount. On the other hand, Cases 7, 11, 12, 18 showed percentage increases of from 35 to 80. The increase in each case was associated with an increase in the total amount of urine. Two cases (4, 20) showed an increased excretion of urea with a decrease in the total amount of urine.

5. *The relation of the increase in the urea concentration to the fall in blood-pressure* is brought out in the following table:

TABLE II.

Case No.	Fall in Systolic Pressure. (mm. of mercury.)	Fall in Diastolic Pressure.	Fall in Pulse-pressure.	Percentage Increase in Urea Concentration.
1	60	20-30	40	65
2	32	20	12	27
3	36	12	24	28
4	14	6	8	75
5	24	15	9	35
6	20	10-15	5-10	15
7	50-70	15-20	35-50	38-83
8	12	+10	2	-6
9	34	8	26	23
10	70	15	55	153
11	30	15-20	10-15	7
12	20	5-10	10-15	33
13	40	15-25	15-25	29
15	30	5-10	20-25	0
16	25	0	25	4
20	30-40	5	25-35	27
21	40-50	5-10	35-40	48

Cases with a large systolic fall (Cases 1, 7, 10, 21, especially) showed the biggest percentage increase in the urea concentration.

6. *Relation of the height of the systolic blood-pressure to the blood urea content.* No definite relationship is observable between the amount of urea in the blood and the height of the blood-pressure.

TABLE III.

Relation of Changes in Urine Volume to Pulse-pressure Changes.

Case.	Change in Pulse-pressure. (mm. of mercury.)	Change in Vol. of Urine in c.c. (3-hourly interval after 15 grm. urea.)
1	-40	-230
2	-12	-60
3	-10-24	-98
4	-8	-140
5	-9	-160
6	-5-10	+20
7	0 to +20	-140
	-35	-25
8	-2	-5
9	-20	-10
10	-55	-355
11	-10-15	+240
12	-10-15	+45
13	-15-25	-101
14	-15	+10
15	-5-10	+1
16	-15-25	-23
17	-20	+1
18	0 to 5	+36
20	-25-35	-105
21	-35-40	-147

Cases 7 and 18 showed apparently some increase in the urea concentration, total urea, and volume of urine, while the blood-pressure was not lowered. The cases showing the greatest decrease in pulse-pressure tended to exhibit the greatest decrease in the volume of the urine.

Two factors enter into the determination of the increase in the total urea excreted in cases showing an increase: (a) increased concentration of urea; (b) increased volume of urine. These factors may operate singly or in combination. The increase in the total urea is due to:

- (1) Increased concentration of urea in the urine.

Cases 4, 9, 12, 20.

- (2) Increased volume.

Case 11 (acute nephritis).

- (3) Both factors.

Cases 6, 7, 18.

The slight decrease in the total urea in Cases 3, 5, 10, 21, is associated with a great diminution in the volume of urine excreted.

Two healthy young adults were examined under the same routine observed in the preceding pathological cases. The results are contained in Table IV on pp. 424-5.

Case 22 showed, under the influence of the vasodilator, increased excretion of urine (33 per cent.), increased total urea (22 per cent.), and slight decrease in the urea concentration percentage of the urine. The increased excretion of urea would thus be accounted for by the increased excretion of urine. On the other hand, Case 23 showed a slight diminution in the amount of urine excreted, no substantial change in the total amount of urea, and no diminution in the urea concentration percentage. The variation in the effects on urinary volume in these two cases is in accordance with Cushny's statement (3) that occasionally a slight increase in the urinary volume may be observed, at other times a decrease. These effects are evidently due to the changes in the calibre of the renal vessels. A small quantity may widen them when they are too contracted to allow of the maximal secretion, while on the other hand, if the normal calibre is the optimal, a nitrite may lessen the secretion by lowering the general blood-pressure. When large quantities lower the pressure greatly, they inevitably lead to a lessened secretion or anuria.

In order to exclude the possibility of a retention of blood urea in the early stages of the administration of the vasodilator drug (leading to the increased percentage of urea in the urine), the blood urea was examined about four hours after the drug had been given in the two normal subjects and in the following group of pathological cases dealt with in Table VI.

Cases 22 and 23.

30.10.24. *Liq. trinitrini* 0.ij 3-hourly for 24 hours.

	Case 22.	Case 23.	
	Blood Urea.	Blood Urea.	Time.
31.10.24	25	31	10 a.m.
1.11.24	22	34	10 a.m.
3.11.24	24	32	10 a.m. 15 grm. Urea after 10 a.m.

Liq. trinitrini 0.ij at 3 p.m. and 6 p.m.

29	41	7 p.m.
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TABLE IV.
Observations on Two Healthy Adults.

	Systolic.	Diastolic.	Pulse-rate.	Blood Urea.	Amount in c.c.	% Urea.	Total Amount in c.c.	Total Amount of Urea (gm.).
Case 22. 30.10.24	132 122	74-6 74-8	80	—	90 97 92	2.62 2.52 2.52		2.358 2.444 2.318 7.120 (2.55%)
<i>Liq. trinitrini begun 3.30 p.m. and continued 5-hourly.</i>								
4.50 p.m. 8 p.m.	140-6 140-2	80 76	90 92				279	
31.10.24	120-6 118	80	—	<i>Liq. trinitrini Qij given at noon.</i>	128 116 120	2.30 2.48 2.41		2.944 2.877 2.892 8.713 (2.31%)
1.11.24	118-20	70	78	22	84 88 102	3.11 3.17 2.56	364	2.612 2.790 2.611 8.013 (2.92%)
3.11.24	130-2 124-6	70-4 74-6	78	24	106 131 74	2.16 2.31 2.31	274	2.290 3.026 2.079 7.395 (2.38%)
<i>Liq. trinitrini Qij given 3 p.m. and 7.15 p.m.</i>								
	132-40	70	96	29			311	

Case 28. 30.10.24	128-122	80-74	66	—	185 98 72	1.75 2.52 2.52	3.238 2.470 1.814 7.522 (2.12 %)
Liq. trinitrini Qij given 3.30 p.m. and approximately every 3 hours until noon 31.10.24.							
8.30 p.m.	108-10	78-80	72	Liq. trinitrini Qij, 7.45 p.m.			
31.10.24 12.45 p.m.	108-10	80-4	72	Liq. trinitrini Qij, 12 noon.			
				163 75 60	31	2.07 2.97 3.28	3.373 2.227 1.968 7.568 (2.54 %)
1.11.24	102-5	70	69-70	34	130 76 64	2.41 3.03 3.12	3.133 2.303 1.997 7.433 (2.57 %)
3.11.24	114	78-80	68-70	32	150 72 60	1.97 3.16 3.33	2.955 2.275 1.898 7.228 (2.56 %)
7.20 p.m. 7.45 p.m. 8.30 p.m.	128 (from 114-70) 96	74 60	80 60	41	Liq. trinitrini Qij given 3.30 p.m. and 7.15 p.m.		

As a urea concentration test had been carried out nine hours previously, the small increases in the blood urea at 7 p.m. on 3.11.24 might have been due to the excess of urea in the blood not having been completely excreted. Accordingly the blood urea was estimated on days on which no urea concentration test was carried out and on which the vasodilator drug was administered :

Blood Urea in mg.

Case 22.	11 a.m.	7.30 p.m.	Case 23.	11 a.m.	7.30 p.m.
5.11.24	26	25		25	30
6.11.24	<i>Liq. trinitrini (Qij at 8 a.m. 3-hourly for 12 hours.</i>				
	27	25		30	33
7.11.24	24	21.5		27	31

It would appear therefore possible to exclude as a cause of the increased percentage of urea in the urine the possibility of a retention of blood urea in the early stages of the administration of the vasodilator drug in healthy subjects. The excess of urea in the blood resulting from a dose of 15 grm. urea does not appear to be excreted completely in nine hours in the case of the healthy subjects considered above, although the residual amount is small.

The above observations with regard to the blood urea content in the early stages of the vasodilator administration were repeated on six subjects with raised blood-pressure. There was no evidence of an early retention of blood urea, which might conceivably have been a factor in the increased percentage of urea in the urine.

The total amount of urea excreted daily was examined in two healthy cases and in two high blood-pressure cases before and during the administration of vasodilator drug, no urea being given.

TABLE V.

	Normal Day.			Day with Vasodilator Drug.		
	Total Urinary Urea in	Amount Urine in	Blood Urea in	Total Urinary Urea in	Amount Urine in	Blood Urea in
	gm.	c.c.	mg.	gm.	c.c.	mg.
	(1)	(2)	(3)	(1)	(2)	(3)
Case 22 (healthy)	12.1	906 (12 hours)	26-25	18.0	1173	27-25
Case 23 (healthy)	12.3	453 (12 hours)	25-30	12.6	400	30-33
Case 24 (high pressure)	23.6	1770	83	26.5	2169	85
Case 25 (high pressure)	8.7	379	38	20.4	680	33
	Day after.			Four Days after.		
	Total Urinary Urea in	Amount Urine in	Blood Urea in	Total Urinary Urea in	Amount Urine in	Blood Urea in
	gm.	c.c.	mg.	gm.	c.c.	mg.
	(1)	(2)	(3)	(1)	(2)	(3)
Case 22 (healthy)	15.2	1246	24-22	14.7	837	—
Case 23 (healthy)	13.9	700	27-31	13.7	720	—
Case 24 (high pressure)	27.8	2745	82			
Case 25 (high pressure)	19.2	727	33			

The amount of urea in the blood was not substantially changed, and the amount excreted in the urine was not diminished in any of the above cases.

The following table, in addition to giving the blood-urea, urinary volume, urea concentration test result, range of the urea percentage, and total urea of the individual specimens of urine in Cases 24 and 25, gives the results observed in four additional high blood-pressure cases where the vasodilator erythrol tetranitrate was given for longer periods up to seven days without any administration of urea. The object of this is to show the effects of the vasodilator apart from any disturbance caused by the artificial introduction of urea into the circulation in the application of the urea test.

TABLE VI.

	Blood-pressures.	Amount Urine in c.c. (24 Hours).	Total Urea in grm.	% Urea in Individual Specimens.	Blood Urea in mg.	Urea Concentration Test %.
Case 24. M. 46	240-160	1770	23.6	1.06-1.63	83	1.25
	220-150	2169	26.5	1.03-1.52	85	
		2475	27.8	0.92-1.42	82	
Case 25. F. 46	220-110	379	8.7	1.3-2.8	38	2.7
	210-105	680	20.4	2.9-3.2	33	
		727	19.2	2.51-2.7	33	
Case 26. M. 63	180-60	760	24.7	2.9-3.3	83	3.0
		(25 hours)	(25 hours)			
		1234	32.5	2.1-3.4		
		1025	29.7	2.7-3.1		
		1097	26.6	1.4-3.05	44	
Case 27. F. 47	148-88	773	6.5	0.81-0.93	50	0.75
		806	8.3	1.01-1.06		
		811	7.0	0.77-0.96		
		1200	7.8	0.6-0.85	50	
Case 28. M. 50	203-130	1672	15.3	0.8-1.24	43	—
		1192	17.5	0.76-2.31		
		1380	21.1	0.56-2.25		
		1625	19.2	0.4-1.81		
		2257	20.1	0.65-1.65		
		980	15.4	1.03-1.84		
	170-118	1180	18.1	0.94-2.06	43	
Case 29. F. 47	205-105	300	7.5	2.5	59	3-3.5
		(10 hours)	(10 hours)			
		545	16.2	2.56-3.11		
		530	13.0	2.0-2.7		
		313	6.5	1.9-2.15*		
		745	10.4	1.4-1.2		
		843	13.4	1.4-1.7		
		889	15.6	1.4-1.8	52	

* E. N. stopped on account of headache.

Remarks.—Case 24. Liq. trin. \mathcal{Q} ij 3-hourly; showed early intolerance to erythrol tetranitrate.

Case 25. Liq. trin. \mathcal{Q} ij 3-hourly.

Case 26. Erythrol tetranitrate gr. i 4-hourly.

Case 27. Erythrol tetranitrate gr. i 4-hourly.

Case 28. Erythrol tetranitrate gr. i t.d.s.

Case 29. Erythrol tetranitrate gr. i 4-hourly.

Cases 24 and 29 showed an early intolerance to the vasodilator drug, and the latter in addition showed a very marked reduction in the amount of urine and urea excreted.

[O. J. M., July, 1926.]

G g

With regard to the general effects of lowering blood-pressure, it was exceptional to get any evidence of disturbance in the condition of the patient, except in the cases where the vasodilator drug was used in the larger doses over a longer period. Occasionally slight palpitation and headache were complained of in one or two cases. There was no complaint of giddiness or faintness, and no noticeable change in the colour of the face was observed. The chief complaints in the cases exhibiting intolerance to the drug were of pain and throbbing in the head. Pulse and respiration generally were but little affected (as shown by the recorded figures in Table I), being, as a rule, increased very slightly in frequency. Oedema, which was present in two or three cases, was not increased by the use of the vasodilator drug. One case (acute nephritis), which showed a slight amount of oedema, exhibited a marked increase in the amount of urine and urea excreted, and a fall in the blood urea and blood-pressure during the time that the drug was being used; there was disappearance of the oedema. Another case of acute nephritis with a very large amount of oedema was not affected adversely. The amount of urine increased to some extent, although the drug was employed for a period extending over a week. This is suggestive with regard to the question of salt retention, since the latter is readily indicated by evidences of oedema.

Although the effects of a single dose of liquor trinitrini on the systemic blood-pressure are diminished in a hour or so and pass off according to different observers in periods varying up to two and a half hours, the decrease in the amount of urine secreted throughout the three hours after the administration of 15 gm. urea in cases which had been previously under the influence of repeated doses of nitrite, compared with the amount obtained on days on which the test was carried out without the administration of nitrite, suggests that the effects of repeated doses of nitrites on the kidney outlast those of a single dose on the systemic blood-pressure. Erythrol tetranitrate, used in a number of cases, has a more prolonged action. As a result of the above-mentioned decrease in the amount of urine leading to an artificial increase in the specific gravity and urea percentage of the urine, vasodilator drugs should not be given during the application of MacLean's test, although cases giving urea percentages much under 2 are unlikely to show specimens of urine above this percentage even during the administration of the vasodilator drug. In connexion with this an interesting point comes up. For example, in the application of MacLean's test to Cases 1, 7, 10, 17, 21, under normal conditions, the second hourly specimen of urine gives urea percentages of 1.7, 1.2, 1.5, 0.9, 2.1, respectively. During the period of lowered pressure the corresponding figures obtained were 2.8, 2.2, 3.8, 1.4, 3.1. The question arises naturally whether the efficiency of the kidney is indicated by the higher figures, or whether kidneys which under normal conditions give a low urea percentage with MacLean's test can be differentiated further as regards their response to the test under lowered pressure.

The percentage of urea obtained from the highest of the three-hourly specimens of urine after the application of MacLean's test to an individual is

not necessarily the maximum for the kidneys of that individual, since some of the individual specimens of urine obtained (apart from administration of urea) throughout the twenty-four hours contain in many cases as high percentages of urea as those obtained in the test specimens, sometimes even higher, as shown in Table VI, Cases 24, 26, 27. It would appear, therefore, that useful guidance to the power of the kidney to concentrate urea can sometimes be obtained by ascertaining the percentages of urea in individual specimens of urine passed at different periods throughout the twenty-four hours.

Conclusions.

1. In the healthy subjects the diuresis which usually follows the administration of 15 gm. urea may or may not be cut down by drugs of the nitrite series in the doses stated, and the power of the kidney under the above conditions to concentrate urea is not impaired. The blood urea and non-protein nitrogen are not increased.

2. In high-pressure cases the diuresis which usually follows the administration of 15 gm. urea is usually cut down by drugs of the nitrite series in the doses stated.

3. The total excretion of urea following the administration of 15 gm. urea is usually not diminished by the administration of nitrites in doses sufficient to cause a considerable lowering of the high blood-pressures present (falls of 20-60 mm.).

4. The power of the kidney to concentrate urea after the exhibition of 15 gm. urea is not impaired, inasmuch as urine of higher urea concentration is still excreted during the period of lowered pressure, e.g. 2.8, 3.0, 3.5, as compared with 1.7, 2.2, 2.0 respectively, when the test is applied before the lowering of the pressure. It remains to be seen whether (apart from the evidence afforded by the unimpaired total urea excretion) high urea concentration values, e.g. 3.5, 3.8, during the period of lowered pressure are significant with regard to reduction of pressure being warrantable, so far as the kidney is concerned.

5. If vasodilator drugs are given in pharmacopoeial doses as distinguished from the larger doses referred to above, the functions of the kidney as regards the excretion of water, the excretion of urea, and the power to concentrate urea are not diminished.

6. The urea and non-protein nitrogen content of the blood is not increased by the administration of vasodilator drugs over periods ranging from twenty-four hours to more than one week. The increased urea concentration in the urine is evidently not dependent on an increased percentage in the blood.

7. If the larger doses are maintained over a longer period, symptoms of intolerance to the drug supervene long before the stage of suppression of urine. Symptoms of intolerance may arise in different cases where the power of the kidney to concentrate urea is either (1) above 2 per cent., or (2) well below 2 per cent.

8. The excretion of urea was not interfered with by a large fall of blood-pressure in a high-pressure case by venesection.

9. The virtual maintenance of the total excretion of urea during the period of lowered blood-pressure in cases of hyperpiesia indicates that the mechanism of hyperpiesis is not to be regarded as compensatory, at least so far as the excretion of urea and non-protein nitrogen is concerned—a conclusion in accord with the results of some clinical observations as regards phenolsulphonephthalein excretion reported by Gruber (4), and guanidine excretion by Major (7).

10. No definite relationship is observable between the amount of urea in the blood and the height of the blood-pressure.

11. Nitrites should not be administered either prior to or during the application of MacLean's test.

12. Apart from the application of the urea concentration test, useful evidence as to the urea-concentrating power of the kidney may often be obtained from the examination of individual specimens of urine over the twenty-four hours, since in some of such specimens there may be a percentage of urea as high as, or even higher than is shown by MacLean's test.

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A CRITICAL ANALYSIS OF CERTAIN LABORATORY METHODS APPLIED TO THE CEREBRO-SPINAL FLUID IN THE SEROLOGICAL DIAGNOSIS OF NEURO-SYPHILIS¹

By H. FERGUSON WATSON

Introduction.

At the present time, in the routine diagnosis of neuro-syphilis, various other laboratory tests, in addition to the Wassermann reaction, are being applied to the cerebro-spinal fluid; and the cytological examination of the fluid also constitutes an important diagnostic method. The correct diagnostic evaluation of these laboratory methods is, therefore, of obvious importance in the study of syphilitic disease of the central nervous system.

The Wassermann Reaction with Cerebro-spinal Fluid.

According to Dujardin (1921), the presence of the Wassermann reacting substance in the cerebro-spinal fluid of syphilitics is due to an increase of meningeal permeability and not to any intrameningeal formation of this antibody, and any form of aseptic inflammation of the meninges occurring in a syphilitic patient with a positive Wassermann may confer the reaction on the fluid. Weil and Kafka (1911) have shown that in inflammatory conditions haemolysin and complement can pass through the blood-vessels into the cerebro-spinal fluid. Complement has been found in the fluid in cases of general paralysis, in cerebro-spinal syphilis, in meningitis, and in spinal tumour. Flexner and Amoss (1917) effected the passage of immune substances for the poliomyelitis virus from the blood into the cerebro-spinal fluid by injecting horse serum intrathecally. When the Wassermann reaction was first applied to the fluid few positive results were recorded. With the original Wassermann technique a positive result was rare. Thus Plaut (1909) obtained only 6 per cent. in his cases. With more delicate technique and the use of larger quantities of fluid the percentage of positive results has been greater. Plaut (1911) still claims that unless a relatively large amount of cerebro-spinal fluid is used in the test positive results may be missed even in cases of general paralysis. Generally

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with small amounts, e. g. 0.05-0.2 c.c., a much smaller percentage of positive results are obtained, and negative results are frequently recorded if the test is carried out during active treatment. McIntosh and Fildes (1914), however, have stated that non-specific results are obtained with quantities larger than 0.2 c.c. Other authors have found the cerebro-spinal fluid anticomplementary when used in large amounts. According to Browning and Mackenzie (1924), in carrying out the Wassermann test it is unnecessary to heat the cerebro-spinal fluid to 56° C., and they use the fluid instead of normal saline for preparing the antigen emulsion.

It is now well known that in some cases the cerebro-spinal fluid may react positively while the serum is negative. This may occur in (a) syphilis of the brain, and (b) treated cases. According to Boas (1922), the cerebro-spinal fluid in the primary stage of syphilis is always negative. On the other hand, Kryle, Brandt, and Mras (1920) have shown that in some cases of primary syphilis the spinal fluid is positive before the serum. Other authors have observed that syphilis attacks the pia-arachnoid at a very early stage, and assert that changes can be seen in the cerebro-spinal fluid during the late primary and early secondary stages in 30 per cent. of all cases of syphilis. See Plaut, Boas, and Lind (1923), Craig and Collins (1914), Wile (1923).

Kolmer (1923) considers that the Wassermann reaction with cerebro-spinal fluid has its greatest value in tertiary syphilis. In general paralysis the fluid is positive in 96-100 per cent. See Mott (1916), Plaut (1911), Boas (1922). Among other workers there has been greater variation in the results of the Wassermann reaction of the cerebro-spinal fluid in cases of general paralysis. See Marie and Levaditi (1907), Marie, Levaditi, and Yamanouchi (1908), Stertz (1923), Noguchi and Moore (1910), Smith and Candler (1923), Marinesco (1919), Noguchi, Rosanoff, and Wisemann (1923), Morgenroth and Stertz (1907), and Nonne (1921). Nonne states that if large amounts of fluid are used 100 per cent. positive results can be obtained in locomotor ataxia and in cerebro-spinal lues. Boas and Neve (1916) found two negative cases in nineteen of locomotor ataxia.

Globulin Tests.

In a normal cerebro-spinal fluid there is but a trace of protein which consists mostly of globulin. In various pathological conditions there is an increase, but practically no attention has been given to the exact quantity of the proteins or their nature. Mestrezat (1912) holds that the serum albumin is mostly increased in acute inflammatory conditions, and the globulin is increased in syphilitic affections of the cerebro-spinal system.

Hektoen and Neymann (1920) have studied the action of specific anti-globulin and anti-albumin precipitins on cerebro-spinal fluid, and found that in general paralysis both the albumin and globulin are increased, but principally the globulin. Though the increased protein represents more albumin than

globulin, most workers have given greater attention to the latter, and various globulin tests have been applied to the cerebro-spinal fluid, particularly in the diagnosis of neuro-syphilis. The recognized globulin tests are those of Noguchi, Ross-Jones, Nonne-Apelt, Pandey, Kaplan, and the sulphosalicylic-mercuric-chloride. Most authors recognize that no test or group of tests is diagnostic of any disease of the central nervous system; indeed, Levison (1923) lays much stress on the fact that all tests are at times unreliable unless supported by other evidence, and that no one test can be regarded as a final criterion. This author holds that the Noguchi, Ross-Jones, and Pandey tests run parallel in the same case, and he found the sulphosalicylic-mercuric-chloride tests useful in the diagnosis of tuberculous meningitis; early in the course of the disease, when other tests were negative, these two gave positive results.

Grossmann (1925) examined sixty cases, including twenty-eight of general paralysis, and he obtained a positive Wassermann reaction in all the paralytics, while the Nonne-Apelt, Weichbrodt (a modified Pandey test), and Boltz tests agreed with the Wassermann findings. In one case of locomotor ataxia all tests were negative. The remainder of his series consisted of cases of epilepsy, senile dementia, dementia praecox, manic depressive insanity, and the psychoses due to arteriosclerosis and alcoholism. In all of these cases the various tests were negative.

The Noguchi test has the disadvantage that the butyric acid reagent has a pungent odour and requires boiling. The Kaplan test has the same objection. The Ross-Jones and the Nonne-Apelt are tests in which globulin is salted out by ammonium sulphate.

The Ross-Jones test seems to be more used in this country than any of the others because it has no odour and does not require boiling. The Pandey and sulphosalicylic-mercuric-chloride tests have been found by most workers to give reliable results.

Lange Reaction.

Since Lange (1912) introduced the colloidal gold test, much has been written appraising its value in the diagnosis of syphilis of the central nervous system.

Zsigmondy (1901) found that a solution of protein precipitated colloidal gold in the absence of an electrolyte. In his earlier experiments, Lange found in a case of general paralysis that the cerebro-spinal fluid (which contains much albumin), instead of showing a protective effect, as Zsigmondy had observed in the case of other albuminous substances, precipitated the goldsol in the form of metallic gold. Continuing his experiments, he showed that in tabes and in acute meningitis the cerebro-spinal fluid also precipitated the colloidal gold solution, and he differentiated types of reaction designated 'paretic', 'tabetic', and 'meningitic' by means of a series of dilutions of the fluid varying according to the strength of the reaction when tested quantitatively, i.e. with a series of varying dilutions. Lange considered that by his method it was possible to measure the protein content of spinal fluid according to the degree of precipitation.

The German school has long relied on the four reactions of Nonne (1910) in the diagnosis of syphilis of the nervous system: (1) a positive Wassermann reaction of the serum; (2) a positive Wassermann reaction of the cerebro-spinal fluid; (3) globulin increase; (4) pleocytosis, to which the Lange test was added.

Miller, Brush, Hammers, and Felton (1915) confirmed Lange's work and showed that the 'paretic' type was constant in general paralysis, but that the 'tabetic' type, now termed the 'luetie' curve, was common to other syphilitic conditions; and also found that such diseases as disseminated sclerosis also gave paretic and luetic curves. Finally, they concluded that not only the paretic curve but also the luetic curve was found in non-syphilitic conditions. Other workers have found the paretic curve in cases of disseminated sclerosis, in encephalitis lethargica, in syphilitic meningomyelitis, and in tabetics with no mental symptoms.

Felton (1917), Fischer (1921), Weston (1920), and, more recently, Anwyl-Davis and Mellanby (1923) with other workers, agree that the globulin is responsible for precipitating the colloidal gold. They conclude that the various types of reaction depend on the relative amounts of albumin and globulin.

German authors conclude that in cases which present the syndrome of Froin (1903) the albumin masks the reaction except in the higher dilutions, and there the change is more one of colour than anything else, and never more than purple or blue. This they term 'Rechtsverschiebung'.

Warwick and Nixon (1920), in an examination of 800 cerebro-spinal fluids from patients suffering from mental and nervous affections, conclude that while the various curves are not diagnostic they are of significance in cerebro-spinal syphilis if taken in conjunction with other laboratory tests. These authors obtained 95 per cent. positive results in the colloidal gold test and 90 per cent. positive Wassermann reactions with the fluid of general paralytics.

Eicke (1913) examined 300 cases and obtained typical reactions in dementia paralytica, secondary syphilis, and meningitis.

Lee and Hinton (1914) obtained colloidal gold reactions in twenty-four cases of tabes, nine of which gave negative Wassermann reactions with serum and cerebro-spinal fluid, and of these, two gave no other positive test with the fluid. In eight cases without involvement of the nervous system, they obtained four positive Wassermann reactions with the serum, but negative results with the cerebro-spinal fluid.

Miller and 'Levy' (1914) examined 210 fluids and found that all cases of general paralysis and tabes gave paretic and luetic reactions respectively; luetic reactions were obtained in thirteen out of fifteen cases of latent syphilis in which there was no clinical evidence of involvement of the central nervous system, and in 80 per cent. of congenital syphilis. They were convinced that the test was more valuable in differentiating the various syphilitic lesions of the nervous system, but were of opinion that it had no advantages over other laboratory tests in congenital, secondary, and tertiary syphilis, and that it did not distinguish between tuberculous and suppurative meningitis.

Grulee and Moody (1913) disagreed with the findings of Miller and Levy in regard to the value of the gold test in congenital syphilis, and drew attention to the fact that these authors had obtained a positive Wassermann reaction in 100 per cent. in this condition.

Lowrey (1917) obtained no positive reactions in non-syphilitic mental cases, but reported 10 per cent. of atypical results.

The Foam Test.

This test does not appear to have been applied to any extent in this country. It depends on the formation and persistence of a foam layer on shaking the tubes; this is of course due to increase of protein. The test has been much used by Levison (1922) and his co-workers. He claims that it is positive in all pathological fluids, but is more marked in acute infections of the meninges. Zingher (1917) described the formation of a heavy foam in acute poliomyelitis, thus corroborating the earlier findings of Levison.

Cytology.

Widal, Sicard, and Ravaut (1903) were the first to show the diagnostic significance of the cell content, and since then this method of investigation has been strongly advocated by others.

Most observers agree with the statement that normal cerebro-spinal fluid seldom contains more cells than 3 per c.mm. Fuchs and Rosenthal (1923) found 0-2 cells per c.mm. Rehm (1923) found 1-5 and even 6-9 per c.mm. Gennerich (1923) found 8 in the fluid of one healthy person; others give the numbers 5-20. Levison (1923) regards the normal fluid as containing 1-6 cells per c.mm., and a count over 6 as suspicious, and over 10 as indicative of some pathological condition. He does not regard every increase of cells as evidence of inflammation of the meninges. Fischer (1921) claims that the cell count obtained by lumbar puncture does not represent that of the cerebro-spinal fluid contained in the ventricle of the brain. On the other hand, Nonne (1924) found no difference.

Normally no blood-cells are present and the type of leucocyte is the small lymphocyte. Large lymphocytes occur infrequently, but their presence raises suspicion. Polymorphonuclear cells are never present normally unless as a result of blood admixture in drawing the fluid.

In syphilitic conditions the increase of cells is due to small lymphocytes. Nonne (1921) observed lymphocytosis in 95 per cent. of general paralysis, in 90 per cent. of tabes, and in 100 per cent. of cerebro-spinal lues.

Ravaut (1907) found pleocytosis in 70 per cent. of cases of secondary syphilis—cases which exhibited no evidence of nervous involvement. Plaut (1911) also noted an increase of cells in the fluid in early syphilitic infection. Altmann and Dreyfus (1913) in 8 primary and 50 secondary cases found pleocytosis in 66 per cent. Zaloziecki and Frühwald (1912), in an examination of 30 cases of early syphilis, recorded 4 with 11-24 cells per c.mm., 5 with 22-87,

and 2 with 94-212. Bergl and Klausner (1912) with 26 cases, of which 4 were in the primary stage, found 17 with pleocytosis (2 of which were primary).

Herrick and Dannenberg (1919) have observed pleocytosis and increase of globulin in cases of pneumonia, influenza, tonsillitis, and the exanthems—all of which showed no evidence of meningitis.

Kryle (1920) noted pathological changes in the fluids of 191 prostitutes, of which 126 gave a positive Wassermann reaction. 117 were examined by neurologists and only 50 showed evidence of nervous involvement. He concludes from his examination of pathological fluids that all cases do not suffer later from disease of the central nervous system.

In considering the value of any laboratory tests, correlation with clinical data is necessary. In certain well-defined conditions the clinical evidence is quite sufficient for diagnostic purposes; in others the personal history is suggestive, and sometimes the laboratory tests alone reveal the nature of the disease, but frequently it is necessary to correlate the patient's history, clinical data, and the results of laboratory investigation. Even then, cases are met with which leave much doubt as to the diagnosis. While certain laboratory tests are known to be more conveniently carried out and more reliable than others, some being simple, some complicated, there is always a danger in placing too much reliance on the more complicated reactions, and for this reason the writer decided to make a critical investigation of tests used for serological diagnosis of syphilis as applied to the cerebro-spinal fluid. A series of 350 cases were investigated as regards personal history, clinical condition,² and the various laboratory tests referred to. Team work has been avoided in order to limit as far as possible the observations to one worker. The laboratory tests were:

1. Wassermann reaction of (a) the patient's serum; (b) the cerebro-spinal fluid.
2. The colloidal gold test with the cerebro-spinal fluid.
3. The foam test.
4. Various tests for increase of globulin.
5. Enumeration of cells, including in most cases a differential count.

The globulin tests performed were the:

- (a) Noguchi. (Butyric acid.)
- (b) Ross and Jones. (Ammonium sulphate.) (Ring Test.)
- (c) Nonne and Apelt. (" ")
- (d) Pandey. (Carbolic acid.)
- (e) Kaplan. (Butyric acid + ammonium sulphate.)
- (f) Sulphosalicylic acid.
- (g) Mercuric chloride.

The investigation is naturally divided into two parts, of which the first part deals with syphilitic and the second part with non-syphilitic cases. In certain cases the author withdrew the cerebro-spinal fluid by cisternal and by ventricular puncture.

² In the purely clinical investigations the writer was associated in all cases with another clinician.

Wassermann Reaction.

The Wassermann reaction was carried out by a modification of the original method. The antigen was an alcoholic extract of heart muscle from a case of congenital syphilis. The extract was saturated with cholesterol, and for the test a 1:10 emulsion was prepared by slow admixture so as to form a markedly turbid suspension. Fixed amounts of antigen (0.5 c.c.) and patient's serum (0.05 c.c.) heated at 55°C. for half an hour were tested with varying doses of guinea-pig complement, and 0.5 c.c. of haemolytic system (sensitized ox red cells) was used. Known negative and positive control sera were always included in each set of tests. The other necessary controls (antigen and serum) were also included. Sera and cerebro-spinal fluids for purposes of uniformity were inactivated for half an hour. The cerebro-spinal fluid was substituted for normal saline in making the antigen emulsion.

The colloidal gold reaction and other protein tests were carried out according to the recognized methods. The technique followed was strictly in accordance with that of the various authors who have described these methods. (See Levison.)

Results.

1. *Syphilitic cases.* Of the 350 cases examined (detailed in Table I), all the laboratory tests were done in a series of 329, while of the remainder the tests unfortunately had to be restricted owing to small amounts of fluid available and to the fact that some of the specimens were not sufficiently fresh for cell counts. 100 of these 329 cases were clinically syphilitic, and the *Wassermann reaction was positive with sera in 96 and with cerebro-spinal fluid in 97.* Few had been under treatment, with the exception of five cases of chronic syphilitic meningitis, three of which gave negative Wassermann reactions with serum and cerebro-spinal fluid, but it is of interest to note that these three cases each gave positive reactions in all tests one month after all treatment had been suspended. These three cases are, therefore, included in the 100 cases of syphilis.

The following table gives an analysis of the results:

		Positive.	Negative.	Doubtful.
<i>Wassermann reaction</i>	with cerebro-spinal fluid	97	3	0
	" serum	96	3	1
<i>Colloidal gold reaction</i>	" cerebro-spinal fluid	89	11	0
<i>Globulin tests</i>	" "sulphosalicylic acid"	95	5	0
	" mercuric chloride	95	5	0
	" Pandey (phenol)	94	6	0
	" Noguchi (butyric acid)	86	14	0
	" Ross-Jones (ammonium sulphate)	71	29	0
	" Nonne-Apelt	71	29	0
	" Kaplan (butyric acid + ammonium sulphate)	71	29	0
<i>Foam test</i>	100	0	0

Cytology. Cells ranged from 9 to 442 per c.mm., and the table on p. 439 illustrates how cells varied.

The Wassermann reaction gave negative results in the three cases of

syphilitic meningitis, already referred to, and a doubtful result was obtained with the serum in one case of neuro-syphilis—a case which presented some indefinite symptoms pointing to early general paralysis, but not definite enough to include it in that category.

The colloidal gold reaction was negative in 2 cases of early general paralysis, in 1 case of interstitial keratitis, in 1 of tabes dorsalis, in 1 of congenital syphilis, in 1 of latent, in 3 cases of syphilitic meningitis, in 1 of neuro-syphilis, and 1 of secondary syphilis.

The sulphosalicylic acid and mercuric-chloride tests gave negative results in 5 instances; 2 cases of hydrocephalus, 1 of congenital syphilis, and 2 of syphilitic meningitis.

The Pandy test was negative in 1 case of secondary syphilis, 2 of hydrocephalus, 1 of congenital syphilis, and 2 of syphilitic meningitis—6 cases.

The Noguchi test failed in the following 14: 2 cases of congenital syphilis, 6 secondary syphilis, 1 neuro-syphilis, 3 hydrocephalus, and 2 syphilitic meningitis.

The Ross-Jones gave negative results in 5 cases of congenital syphilis, 1 of mental deficiency, 8 of secondary syphilis, 1 of neuro-syphilis, 1 of interstitial keratitis, 4 of hydrocephalus, 3 of latent syphilis, 3 of tabes dorsalis, and 3 of chronic meningitis—29 cases.

The Nonne-Apelt and Kaplan showed each 29 failures also. In the former these were made up of 4 cases of congenital, 9 secondary, and 2 neuro-syphilis, 1 interstitial keratitis, 4 hydrocephalus, 2 tabes dorsalis, 1 mental deficiency, 1 pyloric stenosis, 1 atrophic rhinitis, and 4 syphilitic meningitis.

In the Kaplan the negatives included 3 cases of congenital, 9 secondary, and 1 neuro-syphilis, 1 interstitial keratitis, 3 of hydrocephalus, 4 tabes dorsalis, 1 mental deficiency, 1 pyloric stenosis, 2 latent syphilis, and 4 syphilitic meningitis.

An incomplete series of tests was carried out with 21 cases—the Wassermann reaction in all, the colloidal gold test in 19, one or more globulin tests and cell enumeration in 12. Most of these cases had been under treatment. The results are recorded in the following table:

	Positive.	Negative.	No. of Cases.
Wassermann reaction with serum	13	8	21
„ cerebro-spinal fluid	13	8	21
Colloidal gold test „ „ „ „	9	10	19
Globulin test „ „ „ „	11	1	12
Cells	11	1	12

Of these 21 cases, 2 were non-syphilitic (gonorrhoea), 4 were cases of primary syphilis (3 of which had every test negative and were apparently cured, while the other gave negative Wassermann reactions with serum and cerebro-spinal fluid and a negative colloidal gold test; cells were not enumerated nor were globulin tests done, but it is of interest to note that, though the Sachs-Georgi flocculation test has formed part of another extensive investigation and is not yet completed, positive results were obtained with both serum and cerebro-spinal fluid). With 13 cases positive and other 6 accounted for, 2 more fall to

be dealt with. The Wassermann reaction with the serum gave a negative result in a case of general paralysis and a case of latent syphilis, while with the fluid 2 latent cases were negative.

The colloidal gold test was not done in two cases of neuro-syphilis which gave positive Wassermann reactions with serum and cerebro-spinal fluid. A positive result was recorded (lueitic type) in a case of gonorrhoea where every other test was negative. The second case of gonorrhoea gave a negative result, as also did 4 cases of primary syphilis, 4 cases of latent syphilis, and a case of secondary anaemia with slight jaundice.

Globulin tests were done in 12 instances, but not the full series. A negative result was recorded in a case of treated primary syphilis which was negative with every other test. In this case cells were 1 per c.mm. Pleocytosis was present in the remaining 11 cases examined, cells ranging from 10 to 58.

As a result of this analysis 15 cases of syphilis fall to be added to the former 100, giving a total of 115. The Wassermann reaction was done in all, but the colloidal gold test was done in 2 less, and the following table summarizes the results:

		Positive.	Negative.	Doubtful.
Wassermann reaction	with cerebro-spinal fluid	110	5	0
	„ serum	109	5	1
Lange reaction	„ cerebro-spinal fluid	97	16	0

The figures in the other tests remain unaltered, but the following table shows the comparison between Wassermann and Lange tests:

Wassermann reaction	with cerebro-spinal fluid is positive in	95-65 per cent.
	„ serum is positive in	94-78 „ „
Lange reaction	„ cerebro-spinal fluid is positive in	85-84 „ „

The following table gives the cell counts in the syphilitic cases:

Cases.		Average number of Cells per c.mm.	Cells varied between
1	Atrophic rhinitis	20-00	20-
1	Banti's disease	104-00	104-
1	Cerebral gumma	32-00	32-
15	Congenital heart disease	46-10	19-100
2	„ pyloric stenosis	16-50	14-19
1	Eczema oris	19-00	19-
1	Epilepsy	29-00	29-
23	General paralysis	121-69	23-270
10	„ „ (early)	230-01	22-442
2	„ „ (juvenile)	30-50	19-42
3	Hydrocephalus	39-00	19-68
1	Icterus neonatorum	21-00	21-
1	Idiot	139-00	139-
2	Imbecile	26-00	19-33
2	Interstitial keratitis	41-00	15-67
2	Secondary anaemia	33-00	33-
5	Syphilitic meningitis	14-20	10-18
2	Syphilis, condylomata	11-50	9-14
11	„ congenital	22-18	12-39
7	„ latent	18-33	10-39
6	„ neuro-	57-75	13-100
4	„ primary	1-00	0-1
9	„ secondary	20-44	9-64
7	Tabes dorsalis	15-57	12-22

It is specially noteworthy that as a result of this investigation with syphilitic cases the foam test stands first in respect of the constancy of positive results (100 per cent.). The Wassermann reaction, the Pandy and sulphosalicylic-mercuric-chloride tests all correspond fairly closely, with a high percentage of positive results. The Noguchi and Lange tests may be classified together, and the Ross-Jones, Nonne-Apelt, and Kaplan form a class in which the percentage of positive results is lowest. The tests might thus be classified as follows:

	Percentage of Positive Results.
Class I. Wassermann reaction, Pandy and sulphosalicylic-mercuric-chloride tests	94-100
Class II. Noguchi and Lange tests	about 86
Class III. Ross-Jones, Nonne-Apelt, and Kaplan tests	about 71

The detailed list of syphilitic cases (119) is shown in Table II. A synopsis of these cases follows; in it is included a case of trypanosomiasis, making the total number now dealt with 120. Negative cases are considered when they occur in the same group.

Atrophic rhinitis. Cases: one. History: negative. Clinical examination: positive. Lange reaction: negative. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: Noguchi, Pandy, Kaplan, and sulphosalicylic-mercuric-chloride positive; Ross-Jones and Nonne-Apelt negative. Foam test: positive. Cells: 20 per c.mm. Practically all lymphocytes.

Banti's disease. Cases: one. History: negative. Clinical examination: evidence of congenital syphilis. Lange reaction: negative. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: all positive. Foam test: positive. Cells: 104 per c.mm. Lymphocytes 95 per cent.; large mononuclears 4.5 per cent.; plasma cells 0.5 per cent.

Cerebral gumma. Cases: one. History of syphilis while a soldier in India 25 years ago. Clinical examination: not conclusive. Lange reaction: negative. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: all positive except Ross-Jones and Nonne-Apelt. Foam test: positive. Cells: 32 per c.mm. Practically all lymphocytes.

Congenital heart disease. Cases: fifteen. History: all positive. Clinical examination: all positive. Lange reaction: paretic curve in 2; luetic curve in 13. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: all positive. Foam test: all positive. Cells: varied between 19 and 100 per c.mm. Small lymphocytes averaged 90 per cent.; large mononuclears averaged 5.5 per cent.; plasma cells averaged 1 per cent.; polymorphs averaged 3 per cent.; eosinophils averaged 0.5 per cent.

Congenital pyloric stenosis. Cases: three; positive 2; negative 1. History: positive in 1 case. Clinical examination: positive in 1 case. Lange reaction: positive in 1 (luetic curve) and negative in 2 cases. Wassermann reaction: positive with serum and cerebro-spinal fluid in 2 cases and negative in 1. Globulin tests: all positive in 1 case; all positive in another, except Nonne-Apelt and Kaplan, and all negative in the third. Foam test: positive in 2. Cells: 0, 14, and 19 per c.mm. All small lymphocytes except 1 per cent. large mononuclears.

Eczema oris. Cases: one. History: positive. Clinical examination: positive. Lange reaction: negative. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: all positive. Foam test: positive. Cells: 19 per c.mm. Practically all lymphocytes.

Epilepsy. Cases: one. History: positive. Clinical examination: positive. Lange reaction: negative. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: all positive except Ross-Jones. Foam test: positive. Cells: 29 per c.mm. Practically all small lymphocytes.

General paralysis. Cases: thirty-five, of which 10 were in the early stage and 2 were juvenile paralytics. Lange reaction: paretic type and positive in all except 2 of the early cases. Wassermann reaction: positive with cerebro-spinal fluid in all; negative in one serum. Globulin tests: all positive. Foam test: positive in 31; not done in 4. Cells: varied from 19 to 442 c.mm. Small lymphocytes ranged from 85 to 95 per cent.; large mononuclears from 5 to 10 per cent.; plasma cells from 1 to 3 per cent.; polymorphonuclears from 0.5 to 1 per cent.

Hydrocephalus. Cases: five. History: positive in one case. Clinical examination: positive in 2 cases. Lange reaction: very slight change in luetic zone in 4 instances, rising as far as 2 in the other case. Wassermann reaction: positive with serum and cerebro-spinal fluid in 3 and negative in 2 cases. Globulin tests: positive in 3 and negative in 2 cases. Foam test: positive in 3. Cells: 0 and 1 per c.mm. in negative cases and 19, 30, and 68 in the positive. Cells mostly small lymphocytes with 1 to 5 per cent. plasma cells.

Icterus neonatorum. Cases: one. History: positive. Clinical examination: positive. Lange reaction: luetic curve. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: all positive. Foam test: positive. Cells: 21 per c.mm. Practically all lymphocytes.

Idiot with congenital syphilis. Cases: one. History: positive. Clinical examination: positive. Lange reaction: paretic type. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: all positive. Foam test: positive. Cells: 139 per c.mm. Small lymphocytes 89.5 per cent.; large mononuclears 7 per cent.; plasma cells 2 per cent.; polymorphonuclears 1.5 per cent.

Imbecile with congenital syphilis. Cases: two. History: positive. Clinical examination: evidence of congenital syphilis. Lange reaction: luetic type. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: positive. Foam test: positive. Cells: 19 and 33 per c.mm. Except one plasma cell, all are small lymphocytes.

Interstitial keratitis. Cases: two. History: positive. Clinical examination: evidence of congenital syphilis. Lange reaction: luetic curve in one; negative in other. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: all positive, except Kaplan. Foam test: positive. Cells: 15 and 67 per c.mm. Practically all lymphocytes.

Meningitis. Cases: twenty-two. Meningococcal, 9; tuberculous, 8; syphilitic, 5.

Meningococcal. Cases: nine. Fluid slightly olive in 2; turbid in 7. Lange reaction: negative in 9. Wassermann: negative in 9. Globulin tests: all positive with Pandy, Noguchi, and sulphosalicylic-mercuric-chloride. Other

tests had each 5 positive results. Foam test: all positive. Cells: only in 2 cases could cells be correctly enumerated owing to debris; in these cases cells were 1,554 and 1,320 per c.mm. Bulk of cells were polymorphonuclears with a few scattered mononuclears and eosinophils (0.5 per cent.).

It is interesting to observe that no fluid gave a meningitic curve nor any other type.

Tuberculous meningitis. Cases: eight. All were children under 4 years. In one case fluid had a yellow tinge; in this case cells were: polymorphonuclears 0.5 per cent.; large mononuclears 0.5 per cent.; plasma cells 0.5 per cent.; lymphocytes 98.5 per cent. In remainder of cases cells averaged: small lymphocytes 50 per cent.; large mononuclears 5 per cent.; polymorphonuclears 45 per cent. Lange reaction: positive 1; negative 7; in the positive the curve did not rise above 2 and is not a true meningitic curve. Wassermann reaction: all negative. Globulin tests: all positive in 2 and all negative in 3 cases. Partially positive with the remainder. Foam test: positive in 7.

Syphilitic meningitis. Cases: five. All cases had prolonged treatment, and were still under treatment at time of examination. Lange reaction: slight change in 2; negative in 3. Wassermann reaction: positive in 2; negative in 3. Globulin tests: positive in 3 and partially positive in 2. Foam test: positive in 5. Cells: varied from 10 to 18 per c.mm. No polymorphonuclears nor large mononuclears seen; in 2 cases scanty plasma cells observed; remainder small lymphocytes.

Note: One month after all treatment had been suspended the three negative cases gave positive reactions.

Secondary anaemia. Cases: four. History: positive in 2; negative in 2. Clinical examination: doubtful in one case; not conclusive in other, but post-mortem examination leaves no room for doubt. Lange reaction: negative in 3; meningitic curve in other. Wassermann reaction: positive in 2 with serum and fluid. Globulin tests: slight increase in 1; not done in other positive case. Foam test: positive in 1; not done in other. Cells: 33 per c.mm. in one positive; chiefly lymphocytes; not done in other.

Syphilis. Cases: thirty-nine. Condylomata, 2; congenital, 11; latent, 7; neuro-, 6; primary, 4; secondary, 9.

Condylomata. Cases: two. History: positive. Clinical examination: positive. Lange reaction: negative in both. Wassermann reaction: positive with serum and cerebro-spinal fluid in 2. Globulin tests, Pandy and sulphosalicylic-mercuric-chloride: positive in both; with Kaplan and Noguchi: negative in one; positive in the other. Foam test: positive. Cells: 9 and 14 per c.mm. All lymphocytes.

Congenital syphilis. Cases: eleven. History: all positive. Clinical examination: positive in 2. Lange reaction: luetic curve in all. Wassermann reaction: positive with serum and cerebro-spinal fluid in 11. Globulin tests: positive. Foam test: positive. Cells: varied from 12 to 39; chiefly lymphocytes.

Latent syphilis. Cases: seven. History: positive. Clinical examination: positive. Lange reaction: luetic curve in 2, but poor; negative in 5. Wassermann reaction: positive with serum in 6 and with cerebro-spinal fluid in 5. Globulin tests: weakly positive in 6; not done in 1. Foam test: positive in 2; not done in 5. Cells: varied from 10 to 39. All small lymphocytes except an isolated plasma cell in a few instances.

Neuro-syphilis. Cases: six. History: positive in 6. Clinical examination: negative in 2; positive in 4. Lange reaction: paretic curve in 2; luetic curve in 1; negative in 1; not done in 2. Wassermann reaction: positive with all cerebro-spinal fluids. Positive with 5 sera; doubtful with other. Globulin tests: positive in all. Foam test: positive in 4; not done in 2. Cells: varied between 13 and 100 per c.mm. Chiefly lymphocytes with 1 per cent. large mononuclears; no plasma cells.

Primary syphilis. Cases: four. History: positive. Clinical examination: was positive, but negative at time of test. Lange reaction: all negative. Wassermann reaction: all negative with serum and cerebro-spinal fluid. Globulin tests: not done. Foam test: not done. Cells: varied 0-1 per c.mm.

Secondary syphilis. Cases: eleven. History: positive. Clinical examination: positive. Lange reaction: luetic curve in 4; negative in 7. Wassermann reaction: positive in 11 with serum and cerebro-spinal fluid. Globulin tests: partially positive. Foam test: positive in 8; not done in 3. Cells: varied from 9 to 64. Generally lymphocytes, except in one case where polymorphonuclears were 15 per cent. and plasma cells 2 per cent.

Tabes dorsalis: Cases: seven. History: positive. Clinical examination: positive. Lange reaction: luetic type. Positive in 6; negative in 1. Wassermann reaction: all positive. Globulin tests: Noguchi and Pandey positive in 7. Foam test: positive in 7. Cells: 12-22 per c.mm. Cells not greatly increased. Small lymphocytes average 93 per cent.; large mononuclears average 5 per cent.; plasma cells average 1.5 per cent.; polymorphonuclears average 0.5 per cent.

Trypanosomiasis. (This case is not included among those of syphilis.) Cases: one. Fluid supplied from the London School of Tropical Medicine. Patient became insane and died in asylum. Lange reaction: rapid and complete flocculation in all tubes. A type which I have not seen described in the literature. Wassermann reaction: positive with serum and cerebro-spinal fluid. Globulin tests: all strong. Foam test: positive. Cells: 99 per c.mm.; large mononuclears 0.5 per cent.; plasma cells 0.5 per cent.; remainder small lymphocytes, except 2 isolated non-nuclear mulberry-like cells.

Non-syphilitic Cases.

Two hundred and thirty cases are included in this section of the investigation. There was no history of syphilis, nor evidence of it on clinical examination, and the Wassermann reaction with serum and cerebro-spinal fluid was negative in every instance. The colloidal gold test, the globulin tests, and the foam test gave positive results in a number of diseases which are included in the table on p. 444.

Thus, with the exception of chronic nephritis, dental abscess, diphtheria, gonorrhoea, infantile paralysis, mild influenza, mumps, and acute rheumatism, which alone gave reactions with colloidal gold, there is a certain amount of agreement.

No. of Cases.	Disease.	Wassermann Reaction.		Lange.	Noguchi.	Ross-Jones.	Nonne-Apelt.	Pandy.	Kaplan.	Sulphosalicylic Acid.	Mercuric Chloride.	Foam.
		Serum.	Fluid.									
4	Chronic nephritis	—	—	2	—	—	—	—	—	—	—	—
4	Dental abscess	—	—	1	—	—	—	—	—	—	—	—
4	Diphtheria	—	—	1	—	—	—	—	—	—	—	—
18	Encephalitis lethargica	—	—	16	13	12	8	17	9	17	17	17
2	Gonorrhoea	—	—	1	—	—	—	—	—	—	—	—
2	Infantile paralysis	—	—	1	—	—	—	1	1	1	1	1
21	<i>Influenza—</i>											
	Mild	—	—	2	—	—	—	—	—	—	—	—
11	Late	—	—	11	11	6	6	11	6	11	11	11
4	Post	—	—	4	3	3	3	3	3	3	3	3
1	Severe	—	—	1	1	1	1	1	1	1	1	1
	<i>Meningitis—</i>											
9	Acute	—	—	—	9	5	5	9	5	9	9	9
8	Tuberculous	—	—	1	4	2	1	5	3	4	4	7
5	Mumps	—	—	1	—	—	—	—	—	—	—	—
	<i>Rheumatism</i>											
10	Acute	—	—	3	—	—	—	—	—	—	—	—
103				45	41	29	24	47	28	46	46	49

Mumps. A search through the literature of this and other countries shows that pleocytosis may occur in the cerebro-spinal fluid in mumps.

Lavergne (1917) reports the case of a child of 9½ years with tonsillitis and convulsions where polymorphs and lymphocytes were present in equal numbers. Feiling (1913) had a case with 2,500 cells per c.mm. with :

Lymphocytes	96 per cent.
Polymorphs	2 " "
Large hyaline	2 " "

Howard-Tasker (1919) had three cases with 2,500, 703, and 360 cells respectively, of which 90–100 per cent. were mononuclears. Monod, so long ago as 1902, did systemic lumbar puncture in cases of mumps and found pleocytosis. He considered that a meningeal reaction was present in every case at some stage of the disease. De Massary, Tocmann, and Luce (1917) examined the cerebro-spinal fluid of 56 soldiers suffering from mumps and found a pleocytosis in all but 7, and of these only 16 showed meningeal symptoms. Howard, Tessier, and Essmein (1919) have observed a diplococcus in cerebro-spinal fluid in parotitis.

The number of cases examined by the writer was small. Cases: five. Clinical examination: one in early stage and 4 convalescent. Lange reaction:

4 were negative and the one in the early stage gave a luetic curve. Globulin tests: all negative. Foam test: all negative. Cells: 2 cases had no cells, 2 had each 2, while 1 had 305 per c.mm.

Infantile paralysis. Changes in the cerebro-spinal fluid vary with the stage of the disease. In the preparalytic stage, pleocytosis is a constant feature. Cases: two. Clinical examination: disease well established in both patients. Lange reaction: 1 negative; the other showed a very slight mid-zone change. Globulin tests: 1 negative—Kaplan, Pandy, sulphosalicylic acid, and mercuric chloride positive in other case. Foam test: positive in 1 and negative in the other. Cells: 0 in one and 17 per c.mm. in the other, of which 98 per cent. were lymphocytes and 2 per cent. large hyaline.

Chronic nephritis. Cases: four. Clinical examination: disease well established in 2 and advanced in 2. Lange reaction: negative in 2. In one there is a slight change in first two tubes, and in the fourth an atypical change in tubes 2, 3, 4, and 5. Globulin tests: all negative. Foam test: all negative. Cells: 1, 2, 2, and 2 per c.mm.

Dental abscess. Cases: four. Clinical examination: slight swelling in 3; a large swelling in the fourth. Lange reaction: negative in 3; positive in 1, with a meningitic curve of moderate intensity. Globulin tests: all negative. Foam test: all negative. Cells: 1, 2, 3, and 6 per c.mm. The case which gave a colloidal gold reaction showed 1 cell per c.mm.

Diphtheria. Cases: four. Clinical examination: all cases at the second day of treatment. Lange reaction: negative in 3; positive in 1, which gave a meningitic curve. Globulin tests: all negative. Foam test: all negative. Cells: 0, 1, 2, and 3 per c.mm. The case which gave a Lange reaction had no cells per c.mm.

Acute rheumatism. Cases: ten. Clinical examination: all cases showed some polysynovitis. Lange reaction: positive in 3; negative in 7; in 2 there was a typical luetic curve, while a third showed a slight change in the mid zone. Globulin tests: all negative. Foam test: all negative. Cells: 0, 1, and 0 in the cases which gave a colloidal gold reaction.

Encephalitis lethargica. Cases: eighteen. History: all positive. Clinical examination: all patients had been seriously ill for over 1 month, but 1 case which gave negative results had been ill for over 3 months. Lange reaction: paretic curve in 15 and luetic in 1. Globulin tests: except in 1 negative case the tests were more or less positive. Foam test: positive in 17 and negative in 1, where all other tests gave negative results and cells 4 per c.mm. Cells: 4 and 23 in 2 negative cases; varied from 12 to 32 in 16 positive cases; in three instances only were cells over 20 per c.mm.

Influenza. Cases: thirty-seven.

Mild influenza. Cases: twenty-one. Lange reaction: atypical Lange curve in 2 showing changes in first four tubes in one instance and in first three in other. All other tests are negative, but cells are 4 and 2 per c.mm. in these 2 cases.

Late influenza and severe. Cases: twelve. Lange reaction: positive in 5. Globulin tests: Noguchi, Pandy, sulphosalicylic acid, and mercuric chloride tests positive with 12; Ross-Jones, Nonne-Apelt, and Kaplan positive with 7. Foam test: positive with 12. Cells: varied from 12 to 90 per c.mm. Pleocytosis

consisted of the mixed type, with an average of 75 per cent. polymorphs, and the remainder small lymphocytes and large hyaline in almost equal proportions.

Post-influenza. Cases: four. Clinical examination: the patients presented no definite symptoms but remained more or less neurasthenic and lethargic. Lange reaction: paretic curve in 4. Globulin tests: all positive in 3; all negative in 1. Foam test: positive in 3; negative in 1. Cells: 5 per c.mm. in negative case and all polymorphs; 98, 101, and 115 in 3 cases. Polymorphs were 82 per cent., with large hyaline 15 per cent., the remainder being lymphocytes, eosinophils, granular corpuscles, and macrophages.

Of the 230 non-syphilitic cases, the colloidal gold test showed some change in 45 cases, the sulphosalicylic acid and the mercuric chloride in 46 each, the Pandey in 47, and the Foam test in 49. The Noguchi test was positive in 41, Ross-Jones in 29, Kaplan in 28, and Nonne-Apelt in 24. Thus the Pandey and sulphosalicylic-mercuric-chloride tests are practically equal and form Class I; Noguchi with a lower percentage of positive results falls into Class II, but the Ross-Jones, Nonne-Apelt, and Kaplan in Class III (*vide supra*).

The following table gives a summary of the findings with the various tests:

	Positive Reactions.	Negative Reactions.	Not tested.
Wassermann reaction of serum	0	230	0
" " " cerebro-spinal fluid	0	230	0
Lange " " " cerebro-spinal fluid	45	185	0
Noguchi " test with cerebro-spinal fluid	41	189	2
Ross-Jones " " "	29	201	2
Nonne-Apelt " " "	24	206	2
Kaplan " " "	28	202	2
Pandey " " "	47	183	2
Sulphosalicylic-mercuric-chloride " " "	46	184	2
Foam " " "	49	181	2

Discussion.

The majority of serologists consider that in Wassermann technique unheated cerebro-spinal fluid intensifies the reaction, and some believe that if too great amount is used in the test, anticomplementary effects are elicited; on the other hand, complement and haemolysin (to sheep's red blood-cells) are never present in normal fluids, but can be demonstrated in the majority of pathological fluids, especially those of syphilitic origin. The fluid in this investigation was heated so as to ensure uniformity when compared with the inactivated serum of the same patient, and the results suggest that heating the cerebro-spinal fluid to 55° C. does not interfere materially with the diagnostic results.

The results of this investigation in syphilitic conditions are in accord with those of most other workers, and show that in early infections the cerebro-spinal fluid, like other body fluids, contains the Wassermann reacting substance

soon after the disease becomes generalized; and the presence of a positive reaction with the cerebro-spinal fluid is probably not indicative of disease of the central nervous system in every instance. Browning and Mackenzie (1923), however, say that a positive reaction of the spinal fluid test indicates syphilis of the nervous system.

Cases under treatment are known to react negatively—especially in the case of the serum—but in my series the fluid was negative also. When treatment was suspended for a month the reactions again became positive both with serum and cerebro-spinal fluid. This is a rather important consideration for clinicians, and may help to explain, in part at least, some of the reasons for divergent results when the patient's serum, or fluid, is tested at regular intervals and the treatment is intermittent.

With regard to protein increase, this investigation was chiefly confined to the globulins and to a comparison between the various recognized tests. There is much need for further investigation concerning the types of protein that are increased, and more accurate chemical methods for estimating the exact quantity; while more information is required with regard to the role of euglobulin, pseudo-globulin, fibrinogen, haemolysin, complement, and perhaps albumin, which in its proportion to globulin sometimes, according to Levison, reaches 12-1 (in acute meningeal conditions) and 7-3 in general paresis. Such comparisons would probably prove to be not only an interesting investigation, but might throw fresh light on diagnostic methods. In my series the globulin findings, though varying somewhat with the different tests, agree in general with the findings of most other workers.

Reference has already been made in this paper to allowing the precipitates in the sulphosalicylic acid and mercuric chloride tests to stand for 24 hours in order to compare the amounts. It was found that alkaloid and metallic precipitants behaved differently with tuberculous and meningococcal conditions. In tuberculous meningitis the precipitate with mercuric chloride was never less than twice as heavy as that with sulphosalicylic acid, while in meningococcal meningitis the heavier precipitate was with the alkaloid. These results were constant; their importance is obvious, and they confirm the findings of Tashiro and Levinson (1917). Their observation to the effect that general paralysis sometimes shows a greater precipitate with mercuric chloride was also confirmed, but as the result was not found to be invariable its diagnostic value has less significance.

Increase of protein may occur alone or it may be associated with cell increase. Any form of meningeal inflammation may cause this. In syphilitic conditions protein and cells frequently show some degree of relationship, though the rule is not absolute, except perhaps in well-established untreated cases of general paralysis. It cannot be too strongly emphasized that if workers are to have uniform results some standard method for cell enumeration must be accepted. In the French method the fluid is centrifugalized and a smear is made on a slide; the other method in common use is that of the counting-cell.

Several varieties of chamber are in use, (1) the Thoma-Zeiss, (2) the Neubauer, (3) the Nageotte, (4) the Glaubermann, and (5) the Fuchs-Rosenthal. The French method is far from accurate because the size of drop may vary; it is not possible even under the most favourable circumstances to ensure uniform thickness in the smear, and it should be remembered that the velocity of the centrifuge and the shape of the tube affect the nature of the deposit; altogether it is a somewhat 'rough and ready' method without much to recommend it except, perhaps, that the type of cell can be studied on the same slide. The Glaubermann and Fuchs-Rosenthal chambers give more accurate results than the Thoma-Zeiss. Precise cytological methods cannot be overrated, because we know that modern methods of treatment and frequent lumbar puncture have the effect of reducing the cells, but while this is so there is a type of syphilis which defies reduction of cells to the normal. My results are comparable with those of workers who have used the same methods, or at least have clearly indicated the method used.

The value of the Lange colloidal gold reaction is probably over-estimated. It is of less diagnostic value than the Wassermann reaction and its routine application seems hardly justified. It would be unwise to use it as a substitute because other workers have shown that paretic and luetic curves are not confined to syphilitic conditions but have been obtained with encephalitis lethargica and disseminated sclerosis, while in my series acute rheumatism, influenza, and mumps have to be added to the list. The results of this investigation show that in certain other non-syphilitic conditions, e. g. infantile paralysis and nephritis, the luetic curve is less definite, yet definite enough to suggest that future investigators may be able to demonstrate that there are non-syphilitic conditions, other than those found by the writer, which will lead to confusion if too much reliance is placed on this protein test.

Summary and Conclusions.

A careful evaluation has been made of certain tests applied to the cerebro-spinal fluid in the laboratory diagnosis of neuro-syphilis—the Wassermann reaction, the Lange colloidal gold test and various other protein tests, and cell enumeration.

The Wassermann and Lange reactions of the cerebro-spinal fluid were carried out in a series of 350 cases, of which 119 were syphilitic, while various globulin tests and cell enumeration were made on 329.

The Wassermann reaction with the serum and cerebro-spinal fluid was negative in the 230 cases where syphilis could be excluded. In the clinically syphilitic cases the Wassermann reaction gave positive results with the cerebro-spinal fluid in 95.65 per cent., and with the serum in 94.78 per cent., while positive results with the colloidal gold test were obtained in 85.84 per cent. As regards globulin tests, the Pandey, mercuric chloride, and sulphosalicylic acid

gave approximately 95 per cent. positive results; the Noguchi, 86 per cent.; and the Ross-Jones, Nonne-Apelt, and Kaplan, 71 per cent.

Pleocytosis has also been investigated and the results are detailed.

As a result of this investigation it is concluded that:

1. Among these tests the Wassermann reaction gives the highest percentage of positive results in known syphilitic cases and is of most diagnostic significance.
2. The Lange colloidal gold reaction is definitely of less diagnostic value than the Wassermann reaction, giving a much lower percentage of positive reactions in known syphilitic cases.
3. The 'paretic' and 'luetie' types of the Lange reaction are frequently noted in certain non-syphilitic conditions; for example, among those studied, encephalitis lethargica, disseminated sclerosis, acute rheumatism, mumps, and late influenza.
4. The Lange reaction is, therefore, quite unreliable in the diagnosis of neuro-syphilis.
5. In syphilitic conditions, among the globulin tests (Noguchi, Ross-Jones, Nonne-Apelt, Pandey, Kaplan, sulphosalicylic-mercuric-chloride) the Pandey, sulphosalicylic acid, and mercuric chloride tests approximate to the Wassermann reaction in the percentage of positive results obtained.
6. The Noguchi, Ross-Jones, Nonne-Apelt, and Kaplan tests yield in syphilitic conditions a much lower percentage of positives than the Wassermann reaction.
7. In certain non-syphilitic conditions studied, all the protein tests, like the Lange test, may yield positive results.
8. In the syphilitic conditions of the central nervous system studied, the cell enumeration was never less than 10 per c.mm. It is suggested that even such a low count is significant of a pathological state.

A large proportion of these cases was seen in connexion with my official work as Deputy Commissioner in Lunacy, General Board of Control for Scotland, so that clinical examination, recording of history, and the diagnosis were carried out by at least one other medical man; indeed, only cases were accepted for the investigation in which there was entire agreement as regards diagnosis. Certain cases, except where stated, were provided by medical men in general practice.

To both mental specialists and practitioners alike I owe a deep debt of gratitude for the great trouble taken in selecting material and for much valuable assistance in providing facilities for examining the patients.

I am also indebted to Professor Mackie for research facilities granted to me in the Bacteriology Department, Edinburgh University, and to Mr. David Lees, D.S.O., for certain specimens of cerebro-spinal fluid and sera supplied from his clinic in the Royal Infirmary, Edinburgh.

TABLE I.

Adenitis	7	Influenza, post-	4
Anaemia (secondary)	4	" severe	1
Anasarca	1	Interstitial keratitis	2
Banti's disease	1	Malaria	1
Blepharitis	1	Measles	9
Bronchitis	1	Melaena	1
Broncho-pneumonia	1	Meningitis	5
		" acute	9
Cancer of breast and rectum	2	" tuberculous	8
Carditis, acute	13	Mumps	5
" scarlatinal	1	Nephritis, acute	1
Cerebral gumma	1	" chronic	4
Chorea	3	Ozoena	1
Condylomata	2	Otitis media	4
Congenital heart disease	15	Pericarditis	1
" pyloric stenosis	3	Periostitis	1
Coryza	2	Pharyngitis	1
Dental abscess	4	Phthisis	2
Diphtheria	4	Pleurisy	1
Diplopia	1	Pneumonia	3
Eczema	1	Psoriasis	1
" capitis	1	Rat-bite fever	1
" oris	1	Rheumatism, acute	10
Encephalitis lethargica	18	Rhinitis (atrophic)	1
Endocarditis, rheumatic	3	Sarcoma	3
Enteric fever	5	Syphilis, congenital	11
Enteritis	1	" latent	7
Epilepsy	1	" neuro-	6
Gastritis	3	" primary	4
General paralysis, early	10	" secondary	9
" " juvenile	2	Scarlet fever	16
" " late	23	Tabes dorsalis	7
Gonorrhoea	2	" mesenterica	7
Haematemesis	1	Tetanus	1
Hay fever	1	Tetany	10
Hiccough, severe	1	Tonsillitis	1
Hydrocephalus	5	Trypanosomiasis	1
Icterus, catarrhal	3	Typhus fever	1
" neonatorum	1	Whitlow	1
Idiot	1	Whooping-cough	1
Imbecile	2		
Infantile paralysis	2		
Influenza	21		
" late	11		
		Total	350

TABLE II.

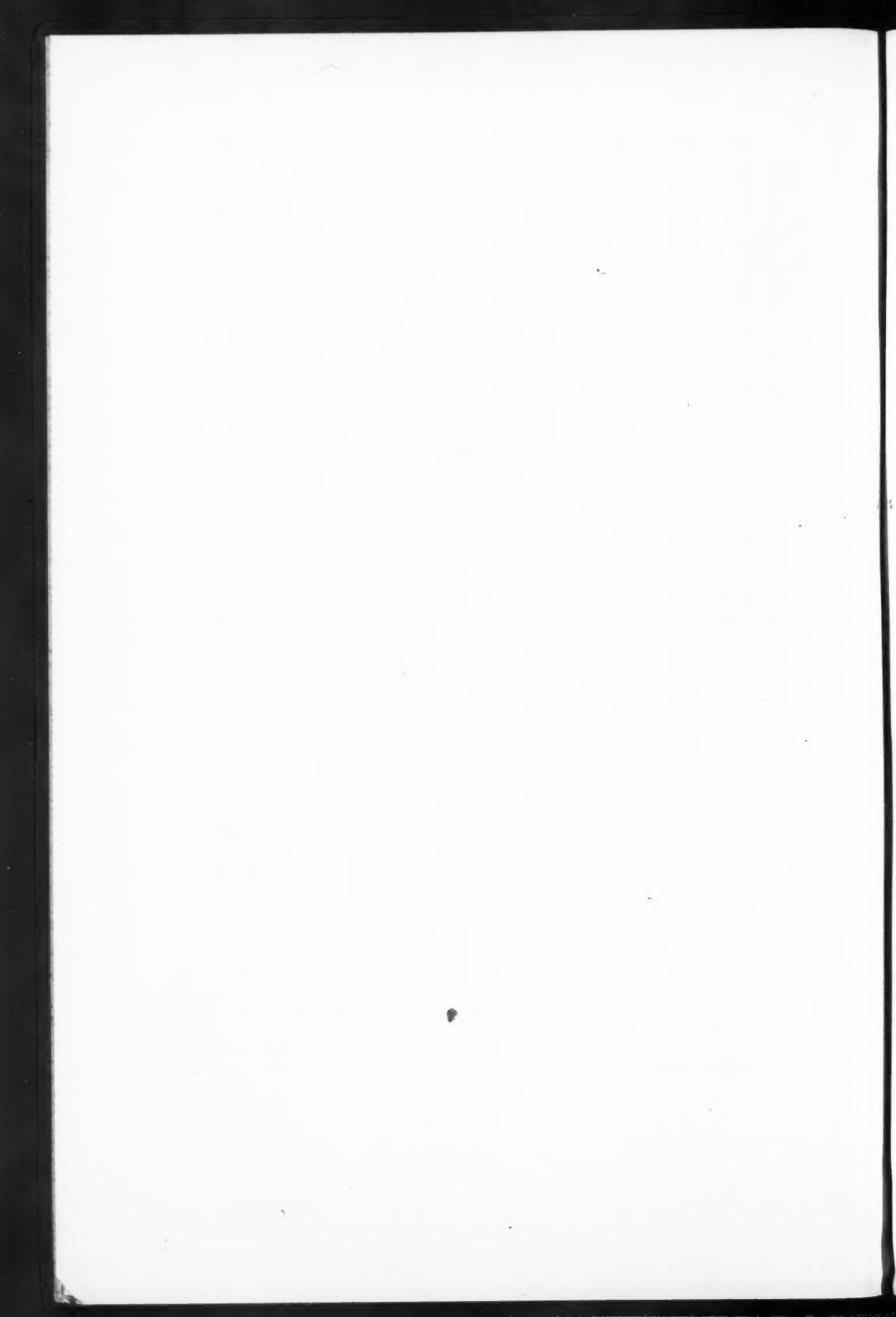
Atrophic rhinitis	1	
Banti's disease	1	
Cerebral gumma	1	
Congenital heart disease	15	
Congenital pyloric stenosis	2	
Eczema oris	1	
Epilepsy	1	
General paralysis	23	
" " early	10	
" " juvenile	2	
	—	35
Hydrocephalus	3	
Icterus neonatorum	1	
Idiot	1	
Imbecile	2	
Interstitial keratitis	2	
Secondary anaemia	2	
Syphilitic meningitis	5	
" condylomata	2	
Congenital syphilis	11	
Latent syphilis	7	
Neuro-syphilis	6	
Primary syphilis	4	
Secondary syphilis	9	
	—	39
Tabes dorsalis	7	
Total	119	

Included in this table are four cases of primary syphilis which were negative to all tests applied in this investigation.

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OBSERVATIONS ON THE GASTRIC ACIDITY AND SECRETION IN HEALTH¹

By T. A. BUTCHER

Introduction.

SINCE the introduction of the method of fractional gastric analysis by Rehfuess (1) in 1914, a large amount of work has been done on the subject, both in America and in this country. The greater part of the fractional analysis in this country has been carried out on pathological cases, and it appears that few investigations have been made on the normal subject, particularly from the point of view of 'psychic secretion' and the effect of various diets on secretory response. In but few cases, also, has sufficient attention been paid to the estimation of total chlorides, and the results are therefore of less value, since it is the curve of total chlorides and not the acidity curve which is the index of the amount of gastric secretion. Bolton and Goodhart (2, 3) have shown the effect of duodenal regurgitation in lowering the curve of free HCl, and emphasized the importance of total chloride estimations. They showed that as the curve of free HCl fell the inorganic chloride curve rose, while the curve of total chlorides remained high, indicating that secretion of HCl was continuing, but that the acid was being neutralized by the regurgitation of alkaline duodenal contents. Baird, Campbell, and Hern (4) in numerous experiments also stressed the value of chloride estimations. These results have been confirmed recently by Morrell Roberts (5).

Bell and MacAdam (6) published the results of twenty consecutive fractional meals performed on the same person, and showed the daily variations in the curve of acidity of a normal individual, but chloride estimations were not performed.

Ryle (7) performed some experiments on himself in order to study the secretory response of the stomach to various food-stuffs, such as gruel, milk, cream, &c.

Bennett and Venables (8) investigated the effect of emotions on gastric secretion and motility. During the experiments, feelings of nausea, hunger, and anxiety were produced in the patient under hypnosis.

In most of the above experiments the standard gruel meal was used, and

¹ Received March 29, 1926.

Technique.

The fractional test meals were all started between 6 and 6.30 a.m. Nothing was eaten or drunk after 10 p.m. the previous evening. The gruel meal, when used, was prepared as described by Crohn and Reiss (9). A quart of water, containing two tablespoonfuls of fine oatmeal, was boiled until the volume was reduced to a pint; the solution was then strained. Immediately before each meal, the fasting juice was withdrawn with a Ryle's tube. After the meal had been taken, specimens of gastric contents were withdrawn quarter-hourly, until the stomach was empty. If, after $2\frac{1}{2}$ hours, the stomach was not empty, the whole of the remaining contents were drawn off and measured. The free HCl and total acidity were estimated by titration with N/10 NaOH, using the dimethyl and phenolphthalein indicators. An estimation of the total chlorides was done on two or three of the samples from each meal, the amounts being expressed in terms of chlorine.

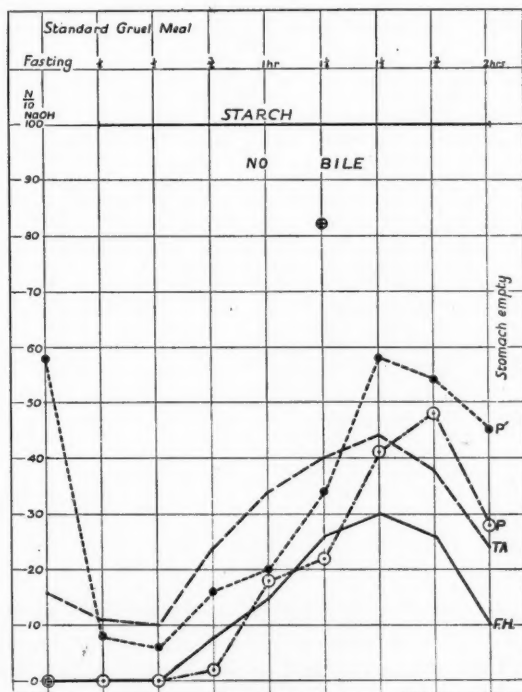


CHART 2.

Psychic Inhibition.

The first meal taken was a standard gruel meal (1 pint). Great and unexpected difficulty was experienced in swallowing the Ryle's tube, and discomfort and nausea were felt throughout the whole meal. The curve obtained (Chart 1) showed an extreme degree of hypo-acidity and gastric inertia.

To become accustomed to the routine of swallowing the tube, the fasting juice was withdrawn daily for ten days, after which time the tube could be passed fairly easily. The gruel meal was then repeated several times, and very constant normal curves were obtained (Chart 2).

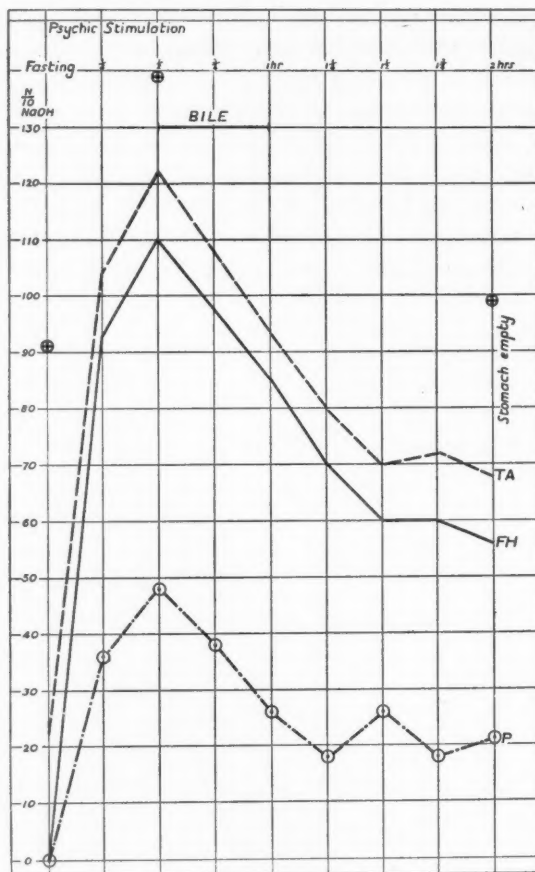


CHART 3.

The first result (Chart 1) may therefore be considered to be an example of psychic inhibition both of secretion and of motility. It bears out the conclusions of Bell and MacAdam that a low acid curve obtained after a first meal may be unreliable, and it is also in agreement with the results of the experiments of Bennett and Venables on the effects of nausea and other emotions produced under hypnosis.

Psychic Stimulation

(a) Experiments were next performed to investigate the secretion of 'appetite juice' in response to psychic stimulation.

Procedure: After the withdrawal of the fasting juice, biscuits were chewed

for half an hour, but were not swallowed. The 'meal' was interrupted for a few minutes, after a quarter of an hour, for the withdrawal of a specimen, and samples were taken every quarter of an hour until no more fluid was obtained. Specimens were clear, contained little mucus, and were easily obtained. The experiment was done on two occasions, with almost identical results (Chart 3). The curves of free HCl and total acid showed a very rapid

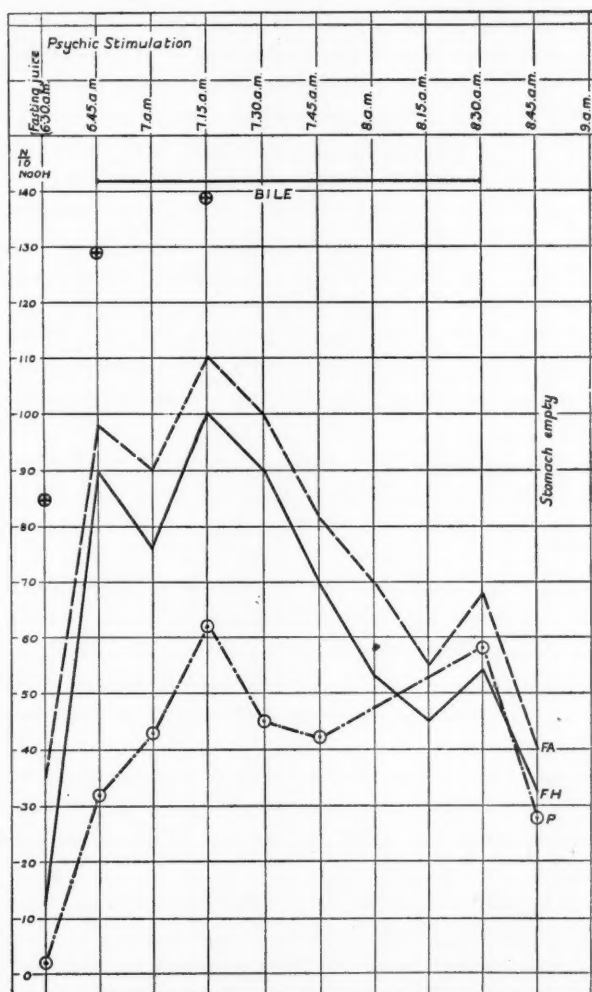


CHART 4.

rise to a high level during the first half-hour, followed by a rapid fall. The stomach was empty on each occasion after two hours. The total chlorides were high. Altogether about 160 c.c. of gastric juice were withdrawn during the two hours.

(b) The next experiment was designed to determine the extent to which gastric secretion was affected by the mere sight and smell of appetizing food.

Procedure: After the withdrawal of the fasting juice, the experimenter fried some sausages for a quarter of an hour. The stomach was then again emptied, and 52 c.c. of juice were withdrawn; this was clear and of high acidity (90 N/10 NaOH). The sausages were then chewed but not swallowed. This was done for half an hour, with a short interruption after a quarter of an hour for the withdrawal of a specimen. Specimens were drawn off every quarter of an hour. A high acid curve was obtained (Chart 4), which resembled that found after chewing biscuits. As in the similar experiments with biscuits, the stomach was empty two hours after the beginning of the 'meal'.

(c) The effect of psychic stimulation was next tried during the course of a standard gruel meal. The experiment was done twice. The standard gruel meal was taken in the usual way, but, one hour after the commencement, the experimenter watched the frying of some sausages for a period of a quarter of an hour. Unfortunately, on the first occasion, the sausages were not very good, and the sight and smell were not as appetizing as usual. In spite of this, however, there was a marked effect on the curve (Chart 5). The curve of acidity is seen to rise considerably higher than usual, and the total chlorides, which were 65 (N/10 NaOH) before the commencement of the psychic stimulation, rose to 99 a quarter of an hour later.

In the second experiment, the 'psychic stimulation' was the frying of bacon and tomatoes. The height of the acid curve was more than double the usual height for the standard gruel meal, and the emptying rate was markedly delayed (3 hours).

These experiments emphasize the importance of the psychic factor in digestion. While it must be admitted that a rise in the curve of free HCl does not necessarily mean increased secretion, the sudden rise in acidity, together with a rise in the total chlorides and in the ferment curve, must be taken as an indication of an increased outpouring of gastric juice in response to psychic stimulation.

The rapid fall in the acid curve (Charts 3, 4) is presumably due to duodenal regurgitation. Possibly this is increased as a result of the inhibition of gastric tonus and motility which is stated by Carlson (10) to occur as a result of gustatory stimuli.

Carlson, as a result of experiments performed on a patient with oesophageal stenosis and a gastrostomy, concluded that psychic stimulation by the sight and smell of food caused no secretion in the stomach, although considerable secretion was produced if the patient chewed and swallowed the food into the stenosed oesophagus.

Action of Atropine on Gastric Secretion.

Evidence has been brought by Bolton (3) and confirmed by Morrell Roberts (5) that the action of atropine on the stomach may be considered to fall under two headings:

- (a) Diminution of secretion;
- (b) Relaxation of the pyloric sphincter.

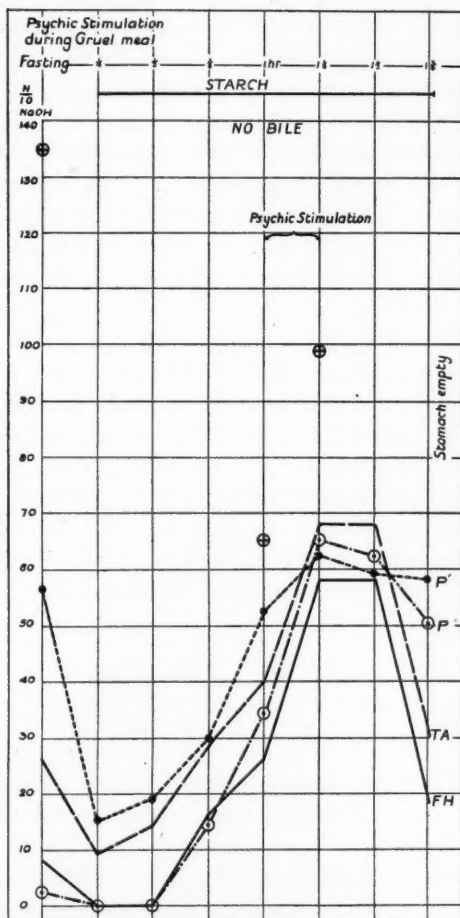


CHART 5.

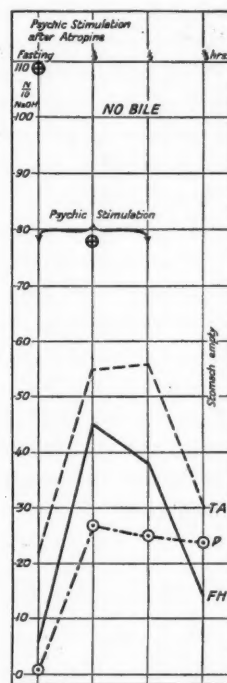


CHART 6.

A few experiments were performed to determine the effect of atropine on the curves of secretion obtained:

- (a) after psychic stimulation (two experiments);
- (b) after a standard gruel meal (two experiments).

Procedure: (a) After the withdrawal of the fasting juice, atropine sulphur

gr. $\frac{1}{80}$ in 100 c.c. water was drunk. After fifteen minutes the stomach was emptied. 75 c.c. of bile-stained fluid were withdrawn on the first occasion; 72 c.c. of clear fluid on a repetition of the experiment. Biscuits were then chewed for half an hour, but not swallowed. Specimens of juice were withdrawn every quarter of an hour. The effects of atropine on the curves were very marked (Chart 6). The free HCl rose to 40-50 only, and no secretion could be obtained after three-quarters of an hour in either of the two experiments. There was also marked lowering of the curve of pepsin secretion (cf. Charts 3, 4).

The fairly high chloride figure of 78 (N/10 NaOH) on this occasion (and 110 on a repetition of the experiment) suggests that the low acidity was due to neutralization by duodenal contents as a result of pyloric relaxation. On comparison with the results obtained in the previous experiments on psychic stimulation (Charts 3, 4), it is seen that the chloride figure, though fairly high, has been considerably lowered by the action of the atropine. This indicates diminished secretion. The fact that no further samples could be obtained after three-quarters of an hour is also in support of this. In the fasting stomach, therefore, atropine causes inhibition of secretion together with relaxation of the pyloric sphincter.

(b) After the withdrawal of the fasting juice, atrophine sulphur gr. $\frac{1}{80}$ in 100 c.c. water was drunk. Fifteen minutes later, a standard gruel meal was taken, and specimens were drawn off every quarter of an hour in the usual way. Very low acid and ferment curves were obtained, the emptying rate was slightly prolonged, and the total chloride figures were lower than normal (Chart 7). The low total chloride figures and the low ferment curves indicate inhibition of gastric secretion by the atropine. The difference between the figure for total chlorides and that for free HCl at one and three-quarters of an hour shows that neutralization by duodenal regurgitation is also a factor in the production of the low acid curve.

The Secretory Response of the Stomach to Various Articles of Diet.

Water: The curves obtained after drinking one pint of water showed considerable variations, both in acidity and rate of emptying. On one occasion, 60 c.c. of juice were withdrawn after two hours; on another, the stomach was empty after one and a half hours (Chart 8).

These results are unlike those published by Bergheim, Rehfuß, and Hawk (11), who obtained very high curves in a similar series of experiments. They considered water to be a powerful stimulant of gastric secretion, and suggested its adoption instead of the gruel meal for fractional analysis. Moffatt, Mitchell, and Powell (12), on the other hand, after successive 'water meals' on the same patient, found low acid curves showing considerable variations in the HCl secretion.

Albumin water. A preliminary experiment was performed to determine the combining power of egg-albumin for HCl. 5 c.c. of egg-white were titrated with

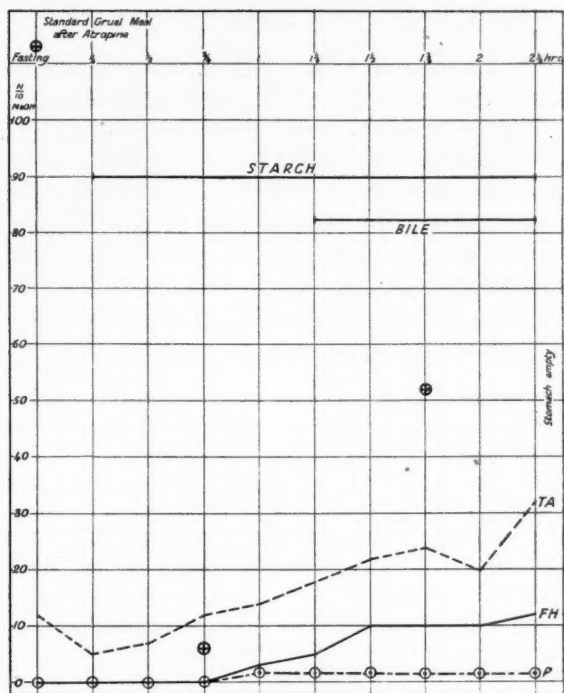


CHART 7.

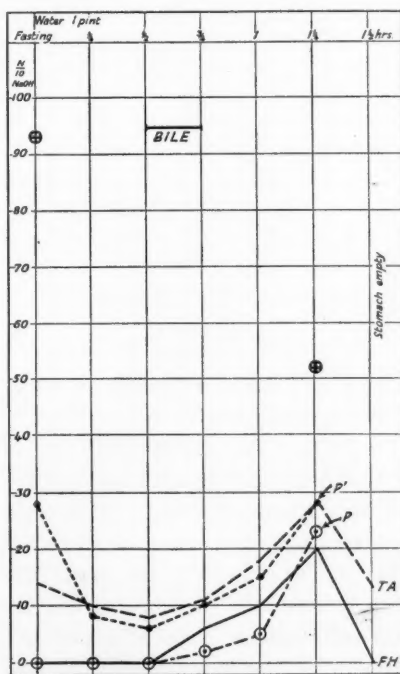


CHART 8.

0.4 per cent. HCl, using the dimethyl indicator. It was found necessary to add 4 c.c. HCl before any free acid could be found in the mixture. Egg-white is thus able to neutralize four-fifths of its own volume of 0.4 per cent. HCl.

A 'meal' consisting of the whites of three eggs well mixed with a pint of water was taken on two occasions. The curves approximated to those found after water alone, the free HCl reaching high points of 30 and 32 in the two cases; but the ferment curves were higher than in the case of the 'water meal'. Unfortunately no total chloride estimations were done in these two experiments.

In view of the high combining power of egg-white for HCl, the above results suggest that egg-albumin causes a certain amount of gastric secretion. This does

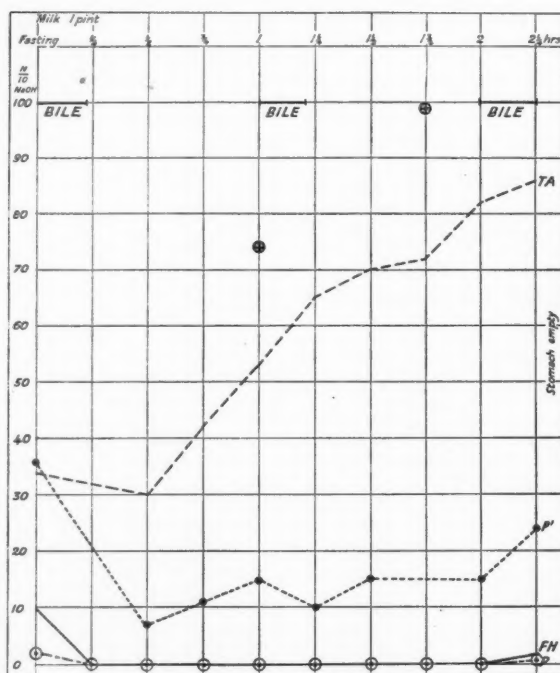


CHART 9.

not agree with the findings of Bateman (13), who considers that egg-albumin does not excite any secretion of gastric juice.

Milk. The results obtained after a pint of milk were somewhat unexpected. The experiment was performed on four occasions, and the curves obtained were almost identical (Chart 9). No free HCl was present in any specimen except the last, in which, on one occasion, there was a small amount only. The curve of total acidity was of the 'climbing' type in each case. The absence of free HCl and the great disparity between the readings for free HCl and total acid were presumably due to the combination of the acid with the milk protein. These results are unlike those obtained by Ryle (7), who found in his own case a fairly

high free acid curve after a milk meal, and a delay in the emptying of the stomach.

Experiments were performed to determine the combining power of HCl for milk protein. 5 c.c. of milk were titrated with 0.4 per cent. HCl, using the dimethyl indicator. It was found necessary to add about 4.5 c.c. of acid before obtaining the pink colour change indicating an acid reaction. As in the case of the egg-albumin, the end point was not sharp, and accurate readings were difficult to obtain. This capacity of milk for neutralizing HCl is a strong argument in favour of its use in conditions of hyperacidity.

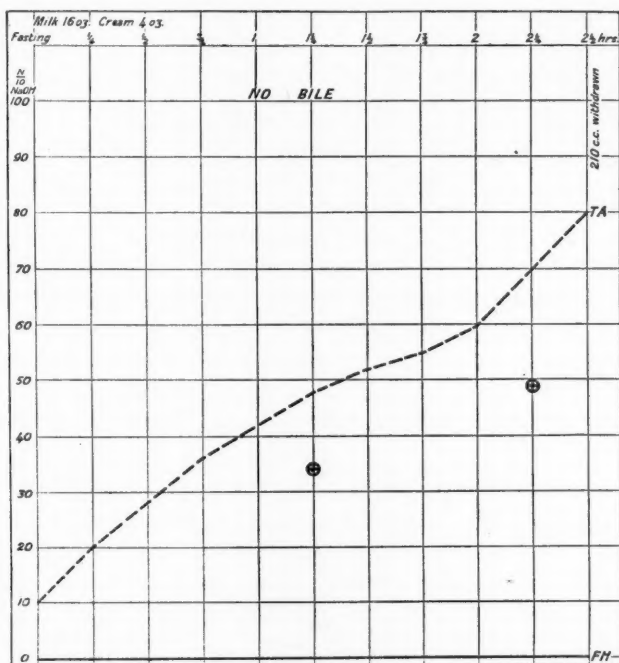


CHART 10.

Fractional analysis after one pint of milk was also done on four other normal men, with very varying results. In one case free HCl was absent in all except the last two tubes, the curve being similar in type to that obtained by the author in his own case; one showed a low acid curve, and the other two showed fairly high curves. In each the curve of total acidity was at a considerably higher level than that of free HCl. In every case the stomach was empty in two hours or less.

Modified milk and milk mixtures. Peptonized milk, milk and cream (Chart 10), milk and brandy (Chart 11), and citrated milk (Chart 12) all gave exactly similar curves, but there was marked delay in the emptying of the stomach in the case of the first three.

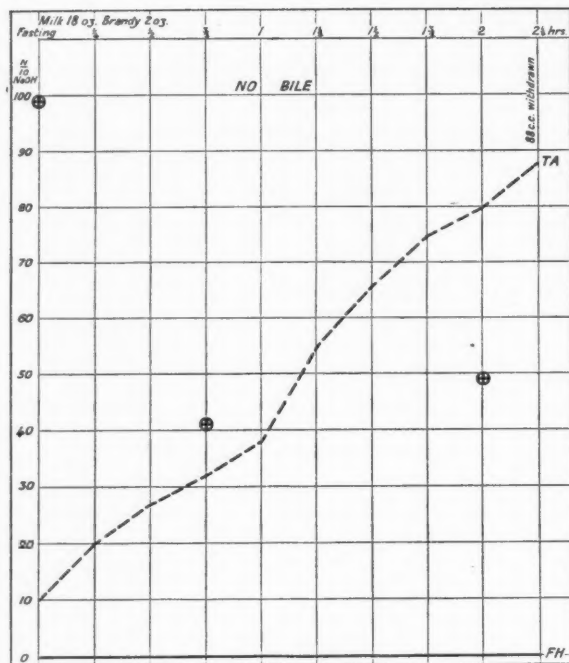


CHART 11.

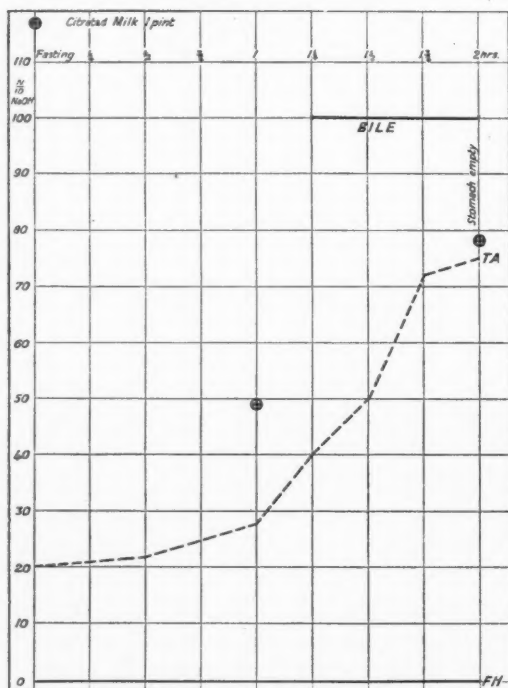


CHART 12.

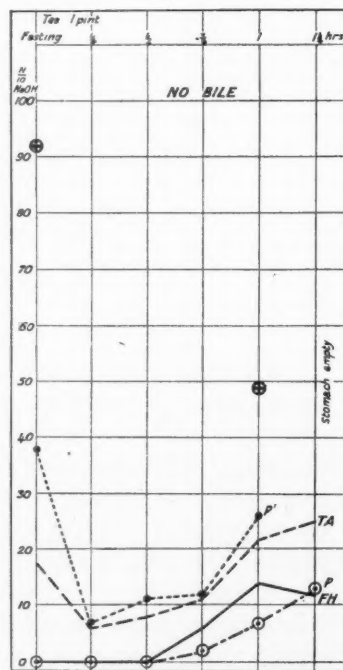


CHART 13.

No less than 210 c.c. were withdrawn two and a half hours after taking one pint of the milk and cream mixture. Diminished secretion, possibly as a result of the extra fat, is indicated by the low total chloride figures in this case.

Tea. Two experiments were done on the response of the stomach to one pint of strong Indian tea. In the first experiment, tea alone was drunk; in the second, a small quantity of milk was added. Two very dissimilar curves were obtained (Charts 13, 14). The difference in the two curves is possibly due to the milk, which made the drink more palatable, and so caused the secretion of a certain amount of 'appetite juice'. The low curve, with low total chloride figures, after tea alone suggests an inhibition of gastric secretion, possibly due to tannin.

Meat extracts. (a) *Bovril.* Fractional analysis after one pint of Bovril was done on two occasions (Chart 15). As with the milk meal, the curve of total acidity was considerably above that of free HCl. This difference was partly due, as in the case of milk, to combination of the HCl with albumin, but also to the fact that Bovril itself has a high figure for total acidity.

5 c.c. of Bovril titrated with N/10 NaOH needed 1.2 c.c. before the solution became alkaline to phenolphthalein, giving an acidity figure of 24 when expressed as a percentage in terms of N/10 NaOH.

(b) *Valentine's meat juice.* A pint of Valentine's meat juice, made according to the directions (1 teaspoonful to 3 tablespoonfuls of water), gave a curve similar to that found after Bovril. Free HCl was absent for the first hour and a quarter, but then rose rapidly to 45 at two hours. The presence of this amount of free HCl would appear to contra-indicate the not infrequent use of Valentine's meat juice after operations on the stomach.

Oil (two experiments). One ounce of olive oil was taken, after the withdrawal of the fasting juice, and a quarter of an hour before taking a standard gruel meal. The curves of free HCl were fairly high (Chart 16) and evacuation was delayed. There was no increase in duodenal regurgitation as shown by the presence of bile, though regurgitation of pancreatic juice without bile may have occurred.

These results are not quite in accordance with those of Lockwood and Chamberlin (14), who, in an investigation on the effect of olive oil on gastric secretion, found, in most cases, a lowering of acidity, delayed evacuation, and an increased regurgitation of bile. They agree, however, with the work of Morrell Roberts (5), who found that fats caused delayed emptying and inhibition of duodenal regurgitation, with a resulting increase in the height of the curve of acidity.

Gruel meal with uncooked currants. This experiment was performed to determine the effect of the addition of some relatively indigestible material to a meal. Two tablespoonfuls of uncooked currants were swallowed without mastication, with the usual gruel meal. While it is impossible to draw definite conclusions on the result of one experiment only, the curves (Chart 17) suggest that the currants, acting as an irritant, caused deficient pyloric relaxation, and

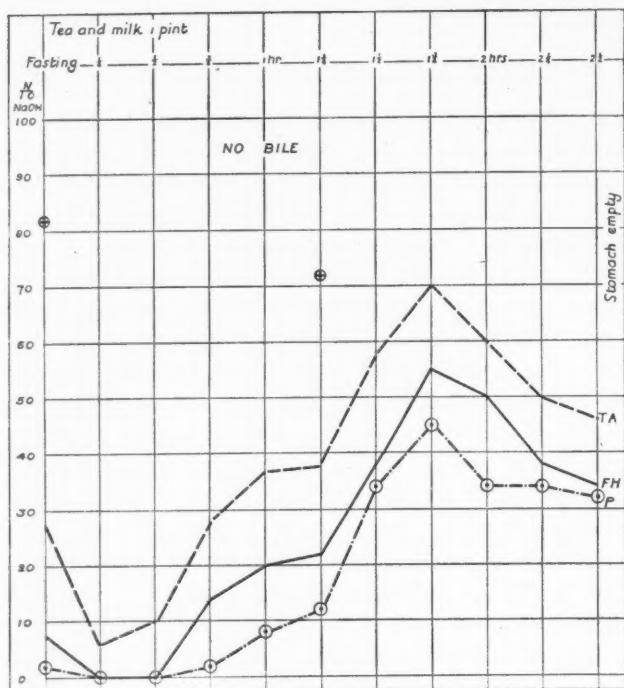


CHART 14.

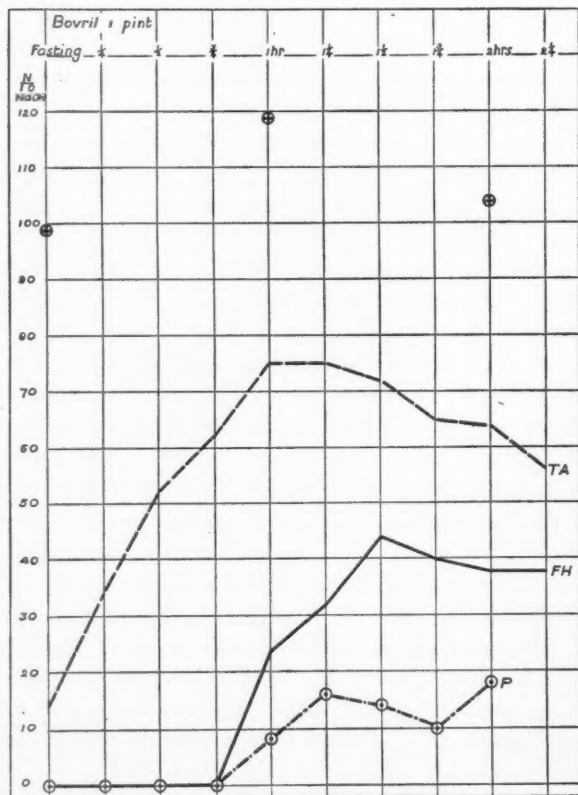


CHART 15.

so produced a 'climbing' type of curve, with delayed evacuation. It is quite certain that this condition of pyloric irritability produced by indigestible food-stuffs is of considerable importance in normal digestion.

Effect of posture. (a) After taking a pint of gruel, the experimenter lay on his right side, and remained so during the whole experiment. A marked increase was found in the emptying rate of the stomach, no further samples could be obtained after $1\frac{1}{2}$ hours. The acid curves were of the 'climbing' type. This result suggests a possible line of treatment for patients with dilated atonic stomachs, not secondary to pyloric obstruction.

(b) The experiment was repeated lying on the left side. The stomach was empty in two hours, i. e. there was no delay in evacuation, and there was nothing abnormal in the curves of free and total acid.

The Fasting Juice.

The fasting juice was withdrawn and examined on fifty occasions, and its composition was found to be as follows:

Quantity: Average, 23.5 c.c.; minimum, 10 c.c.; maximum, 52 c.c.

Free HCl: Average acidity, 3.2; minimum, 0; maximum, 20.0.

On thirty-six occasions (72 per cent.) there was no free HCl in the fasting juice. It was noticed that the fasting juice was more often neutral when withdrawn immediately on rising, than when withdrawn half an hour or so later.

Total acidity: Average, 19.6; minimum, 8.0; maximum, 38.0.

Mucus was constantly present, and on ten occasions was noted as being present in considerable quantity. Bile was present on nine occasions (18 per cent.).

Pepsin. The peptic index, found after bringing each specimen to a constant acidity of 0.2 per cent. HCl (see later), was determined on ten occasions:

Average, 39.2; minimum, 14.0; maximum, 58.0.

Total chlorides, estimated as chlorine, and expressed in terms of N/10 NaOH:

Average, 96; minimum, 66; maximum, 139.

Bacteriology of the Fasting Juice.

The neutral fasting juice, after aseptic removal, was examined bacteriologically on several occasions. On each occasion, sarcinae, streptococci, and staphylococci were grown on agar and in broth cultures. No growth was obtained in MacConkey's medium.

Gastric Secretion during a Fast.

Nothing was eaten or drunk during the course of the experiment, and the gastric contents were withdrawn every hour from 7 a.m. until 8 p.m.

An estimation of free acid, total acid, and ferment content was performed on each sample. The volume of urine secreted was measured hourly, and a urea

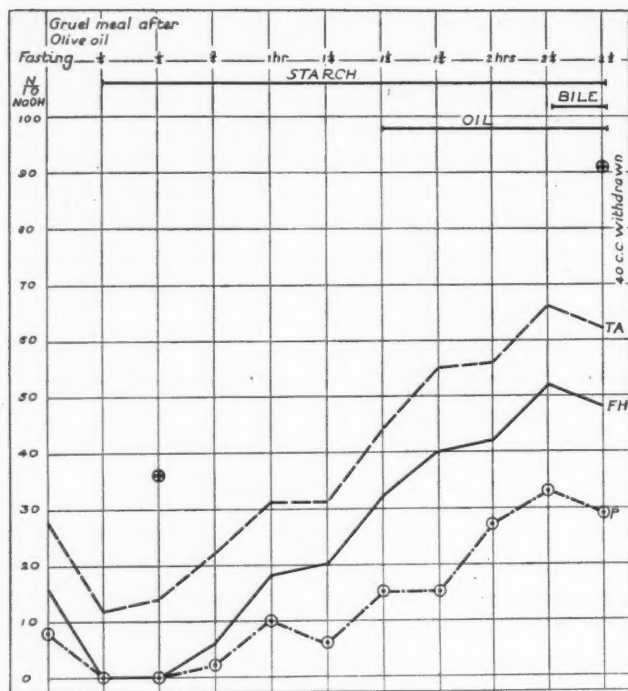


CHART 16.

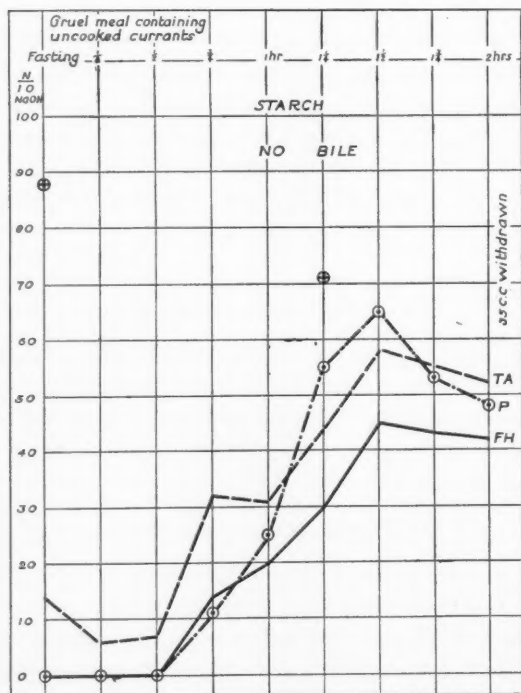


CHART 17

estimation was performed every two hours on the mixed two-hour samples. The results are shown in Charts 18, 19, 20.

During the course of the day, the experimenter performed his usual work as far as possible, and avoided 'psychic stimulation' by the sight or smell of food. No discomfort or hunger was experienced, except during the first few hours, after which time no particular desire for food was felt. It is seen (Chart 18) that although the fasting juice was neutral, the secretion during the day was always acid, and sometimes strongly so. This might be explained on the assumption

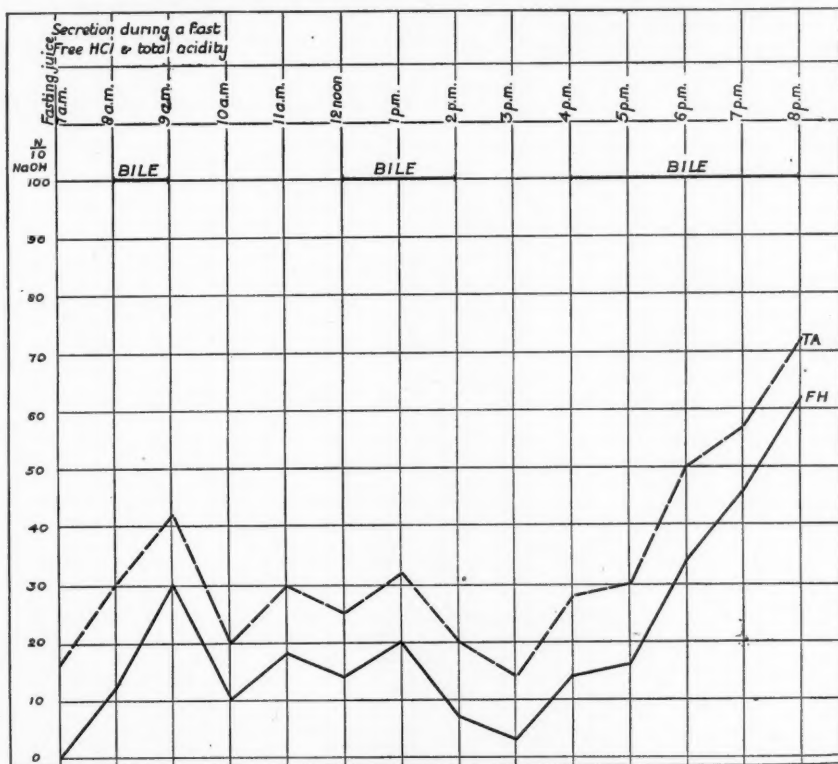


CHART 18.

either that exercise causes the secretion of gastric juice, or that secretion is diminished during sleep, and it certainly appeared to be the case that the fasting juice withdrawn immediately on rising was more often neutral than when withdrawn somewhat later. The free acid for the first ten hours (until 5 p.m.) averaged 14.6. At about this time it was decided to terminate the experiment at 8 p.m. instead of continuing for two days as originally intended. The very marked rise in both the quantity of juice, and in the acidity, during the latter part of the experiment, was presumably caused by 'psychic stimulation', although the experimenter was not conscious of any particular elation at the thought of a meal.

The curves of pepsin secretion (Chart 19) were found to conform closely in shape to those of free HCl. The curve of hourly quantities of urine secreted (Chart 20) appeared approximately to follow the curve of quantities of gastric juice. The urea concentration of the urine showed a maximum of 2.30 per cent. during the first two hours. It fell to 1.45 per cent. during the second and third two-hour periods, and then gradually rose to 2.15 per cent. in the last specimen (Chart 20).

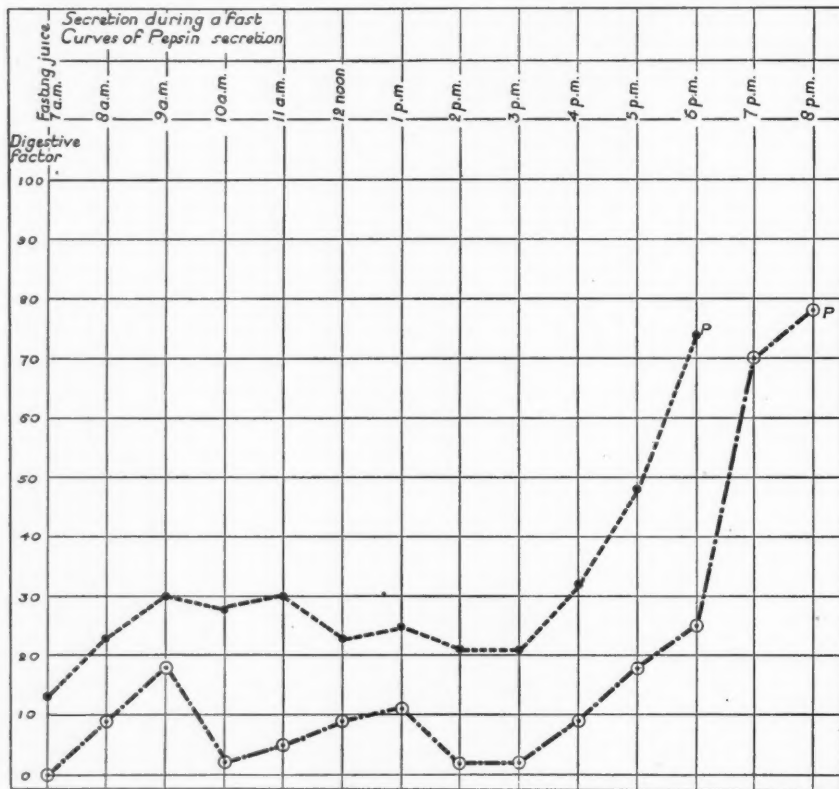


CHART 19.

The experiment was repeated under exactly similar conditions, except that on this occasion the experimenter cycled 25 miles in the course of his day's work. Total chloride estimations were performed on all specimens.

The curves obtained (Chart 21) were similar to those of the first experiment, but ran at a decidedly higher level. The average acidity (free HCl) in the first experiment was 20, in the second 38. This difference may be accounted for by the increased exercise performed on the second occasion.

The Action of Gastric Juice on Blood.

An occasion was chosen when the fasting juice was found to be neutral. Biscuits were then chewed for half an hour, but were not swallowed, and the stomach contents were again emptied. 56 c.c. of juice were withdrawn, with a free HCl figure of 68, and a total acidity of 76. Blood was taken from a vein in the arm, and at once added to each of the above specimens in test-tubes. The sample of acid juice went almost black immediately on addition of the blood. The neutral sample, however, remained bright red, and had become only slightly darker twelve hours later.

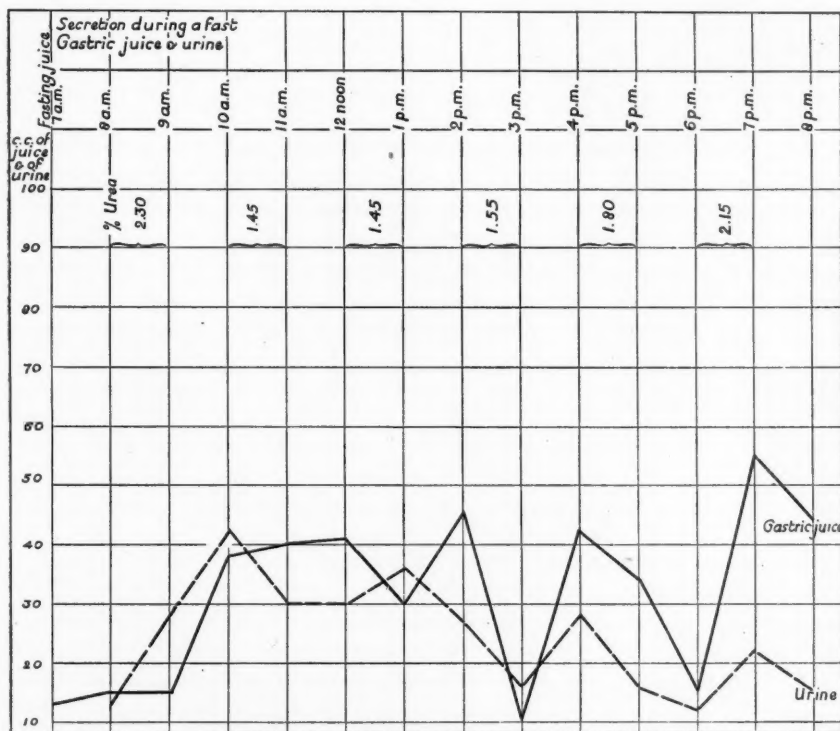


CHART 20.

From this it would appear that the vomiting of bright red blood would not necessarily indicate a recent gastric haemorrhage, if it occurred in the case of a patient who had no free HCl in the stomach, either on account of achylia, or from free duodenal regurgitation. Also, since the majority of cases of gastric ulcer have a high gastric acidity, the vomiting of dark blood may take place immediately after the bleeding has occurred, or even while it is occurring, and does not necessarily indicate an old haemorrhage.

Variations in Acidity in Different Parts of the Stomach.

One and a half hours after the taking of a gruel meal, a Ryle's tube was swallowed until it was considered that it had reached the pyloric end of the stomach. Measurement of the tube and a previous X-ray of the stomach in the erect position made this easier to determine. A sample of gastric contents was then removed. The tube was next withdrawn until the end lay in the fundus of the stomach, and another sample was taken. A difference of ten points was found between the acidity of the fundus and that of the pyloric end. The figures were:

Fundus: free HCl 16, total acid 30, mucus present, no bile.

Pylorus: " " 6, " " 20, " " " "

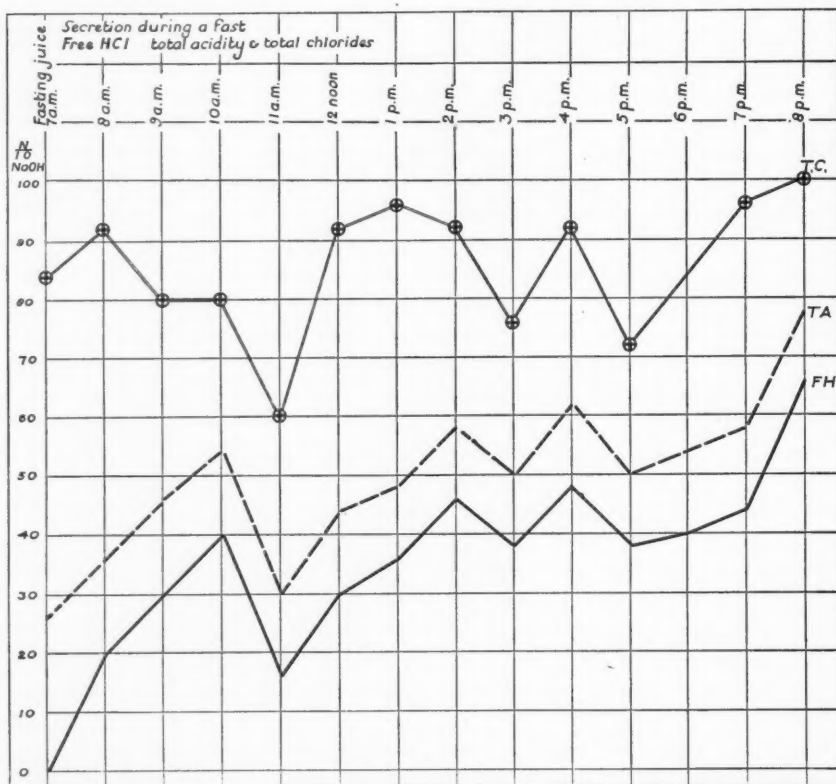


CHART 21.

Such a result has been brought forward as indicating that the whole method of gastric analysis is unreliable. This, however, is not so. While it is evident that there are variations in the acidity of the gastric contents in different parts of the stomach, fractional analysis gives a fair indication of the changes of acidity during digestion, provided that the level of the tube is kept constant during the meal.

Urinary Secretion during Fractional Test-Meals.

On ten occasions the urinary secretion was measured every half-hour during fractional test-meals. It was found that the greatest secretion always occurred during the third half-hour, i. e. between one hour and one and a half hours after taking the meal. As a rule, about 50 per cent. of the secretion during the meal occurred in this period.

The urea content of the samples of urine after a gruel meal was estimated on one occasion.

Urine :	Quantity during 1st half-hour	1½ oz.	Urea	1.80 per cent.
	" "	2nd "	7½ oz.	" 0.35 per cent.
	" "	3rd "	8½ oz.	" 0.2 per cent.

Investigations on the Secretion of Pepsin.

Pavlov (15), in a large number of experiments on dogs, studied the effect of appetite on gastric secretion, and showed the importance of the psychic factor in digestion. He also studied the variations in the digestive power of the gastric juice secreted in response to stimulation by various food-stuffs. Experiments on the secretion of pepsin in the human subject have been carried out by Reh fuss and his co-workers in America, by Ehrenreich (16), and by Aliprandi (17); but it appears that few recent observations on the subject have been made in this country. For the estimation of the concentration of pepsin in gastric contents, most observers have employed the process of Mett, and his technique has been followed, with some variations, by the author.

Mett's Process for Pepsin Estimation.

A piece of fine glass tubing, filled with coagulated egg-white, was placed in the fluid which was to be tested; this was then incubated for ten hours at 37° C. The digestive power of the fluid was determined from the length of the column of egg-white digested from the ends of the tube. Though less accurate than Fuld's Edestin method, or the Ricin method of Jacobi, this process is far less laborious, and appears to be sufficiently accurate for the purpose.

Preparation of Mett's Tubes.

Glass tubing of 2 mm. calibre was broken into lengths of 1½–2 cm. The white of an egg, beaten to break up the membranes, was poured into a test-tube. The small glass tubes were then placed in the egg-white, and left to stand 12 hours to allow bubbles to rise to the top. The test-tube was then placed in boiling water for five minutes, removed, and allowed to cool for three hours. It was then broken, and the albumin tubes were cut out with a sharp knife, care being taken to cut the albumin column cleanly across at the ends of the tubes.

Estimation of Pepsin.

The tubes were next placed in the fluids to be tested, and incubated at 37° C. for ten hours, after which time solution of albumin had occurred at the ends of the tubes. The amount of albumin digested in each was found by subtracting the length of the albumin column from the length of the glass tube. Measurements were made to $\frac{1}{16}$ mm., using a microscope with a sliding-stage and vernier attachment.

The digestive factor was calculated according to the law of Shutz and Borisoff, viz. that the quantity of pepsin in the fluid is proportional to the square of the length of the albumin column digested. Thus, if 5 mm. of albumin were digested, the digestive factor was taken to be 25.

A preliminary experiment was performed to determine whether the solution of egg-albumin in gastric juice occurred at an even rate, or whether it was affected by the products of digestion in the tube. It was found, by taking two-hourly measurements, that, for the first twelve hours, the length of the albumin column digested was proportional to the period of digestion.

It was shown by experiment that the amount of egg-albumin digested by a solution of pepsin depended both on the quantity of pepsin present, and also on the acidity of the solution.

A series of tubes each containing the same amount of pepsin, but with acidities increasing from 0 to 0.2 per cent. HCl, showed digestion of albumin increasing in proportion to the acidity.

It thus appeared obvious that it was impossible to compare the amounts of pepsin present in samples of gastric contents, unless they were all brought to the same acidity. Two estimations of pepsin were therefore performed on each of the quarter-hour test-meal specimens, one on the untreated sample, the other after bringing the acidity to 0.2 per cent. HCl by the addition of acid.

The curves of peptic digestion were found to conform in shape to the curves of free HCl. The curve obtained after bringing the acidity of all specimens to 0.2 per cent. HCl was also of the same shape, but at a higher level, except when the free HCl in the untreated sample rose to 0.2 per cent., at which point the two curves were found to approximate (Chart 5).

Samples of gastric contents not containing free acid gave no digestion of albumin after incubation, but, on addition of HCl to 0.2 per cent., digestion was usually obtained.

Neutral fasting juice was examined for its digestive power on ten occasions. No digestion occurred without addition of acid, but on bringing the acidity of the juice up to 0.2 per cent., an average digestion of 6.26 mm. of albumin resulted, giving a digestive factor of 39.2. This fairly high digestive power appears to be characteristic of the fasting juice in the case of the author.

The samples of gastric contents obtained after a milk meal gave no digestion in any of the tubes except on one occasion (Chart 9), when the last tube showed

a little digestion only ; on addition of acid, however, a fair amount of digestion occurred.

At first sight, it might appear from this that pepsin does not digest milk in the stomach, since it cannot act except in an acid medium. Analysis of the samples, however, demonstrated the presence of albumoses and peptones, showing that pepsin is able to digest the acid-milk-protein compound even in the absence of free HCl.

In the curves obtained after atropine (Charts 6, 7) it is seen that there is a great diminution in the digestive power of the gastric juice as well as in the acidity.

It is thus evident that the curve of peptic digestion, obtained after adjusting the acidity of all samples to 0.2 per cent., is a true expression of the quantity of gastric secretion, and would conform in shape to the curve of total chlorides.

Conclusions.

(a) That nausea and distaste for an article of diet may cause a very great diminution of both gastric secretion and motility.

(b) That the 'appetite juice' is secreted in considerable quantities in response to psychic stimulation by the sight, smell, and taste of food ; and that the secretion continues for some time after the cessation of the stimulus.

(c) That atropine, taken by the mouth, causes diminution of gastric secretion, produced both by the standard gruel meal and by psychic stimulation, together with relaxation of the pyloric sphincter.

No definite conclusions as to the secretion of pepsin can be drawn on the results of so few experiments.

The results obtained suggest, however :

(a) That the curve of secretion of pepsin corresponds in shape to the curve of free HCl, when this is present.

(b) That the curve obtained does not give a true indication of the amount of pepsin present, unless all specimens are brought to the same acidity ; but that if this is done, the height of the curve is proportional to the amount of gastric secretion, and the curve will conform in shape to that of the total chlorides.

(c) That psychic stimulation increases the output of pepsin as well as of HCl.

(d) That atropine, taken by the mouth before a gruel test-meal or before psychic stimulation, diminishes the secretion of both pepsin and HCl.

My thanks are due to Dr. Charles Bolton and Dr. T. R. Elliott for much helpful advice and criticism. I wish also to acknowledge my indebtedness to Dr. G. Goodhart, Dr. A. Lundie, and Mr. C. Dilthey for kindly undertaking the total chloride estimations, and to Dr. F. Hopkins and to my wife for valuable assistance in the experiments.

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ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

THE NINETEENTH ANNUAL GENERAL MEETING was held on Friday, May 29, 1925, at the Royal Society of Medicine, London, at 10 a.m.

The President, Dr. G. Parker, was in the chair.

The minutes of the last General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Election of Officers.

President. Sir Humphry Rolleston, Bart., P.R.C.P., was elected and took the chair. He proposed a vote of thanks to the retiring President, Dr. G. Parker, for his services during the past year.

Treasurer. Sir William Hale-White.

Secretary. Dr. H. Morley Fletcher.

Executive Committee. The following were elected :

Members for England :

Lord Dawson.
Professor F. R. Fraser.
Dr. F. Craven Moore.
Dr. F. J. Nattrass.
Dr. J. A. Nixon.
Dr. H. L. Tidy.

Members for Scotland :

Dr. J. B. M. Anderson.
Dr. W. T. Ritchie.
Dr. J. Mackie Whyte.

Members for Ireland :

Dr. J. S. Morrow.
Dr. G. E. Nesbitt.
Professor W. W. D. Thomson.

Honorary Member. The retiring President, Dr. G. Parker, was elected.

Foreign Honorary Members. On the nomination of the Executive Committee, the following were elected :

Professor A. A. Hijmans van den Bergh (Utrecht).
Professor A. Chauffard (Paris).
Professor W. S. Thayer (Baltimore).

ASSOCIATION OF PHYSICIANS

Election of New Members.

The following were elected :

- Alfred Douglas BIGLAND, M.D., Assist. Phys., Liverpool Royal Infirmary.
Joseph le Fleming Coy BURROW, M.B., Assist. Phys., General Infirmary, Leeds.
Frederick George CHANDLER, M.D., Physician with charge of Out-patients, Charging Cross Hospital.
Ivor J. DAVIES, M.D., Assist. Phys., Cardiff Royal Infirmary.
Anthony FEILING, M.D., Assist. Phys., St. George's Hospital.
Arthur E. MAITLAND-JONES, M.D., Assist. Director, Medical Unit London Hospital.
Henry F. MOORE, M.D., Physician, Mater Misericordiae Hospital, Dublin.
John K. RENNIE, M.B., Physician to Out-patients and Physician-in-Charge of Cardiographic Department, Royal Infirmary, Glasgow.
James Calvert SPENCE, M.D., Medical Registrar, Royal Victoria Infirmary, Newcastle-on-Tyne.
Arnold W. STOTT, B.Ch., Assist. Phys., Westminster Hospital.

Treasurer's Report. Sir William Hale-White presented his balance-sheet, which showed a balance of £217 6s. 11d.

Place of Meeting in 1926. The Secretary read letters of invitation from Newcastle (Dr. Hume), Belfast (Dr. McKisack), and Leeds (Professor Wardrop Griffith). On the recommendation of the Executive Committee it was resolved to accept the invitation from Newcastle for 1926.

Alteration of Rule 20. Dr. G. R. Murray, who had given due notice of motion, moved that in Rule 20 the word *four* be altered to *three*. The motion was seconded and carried with very few dissentients.

SCIENTIFIC BUSINESS. 10.30 a.m.

1. *The effect of Trauma on the distribution of the lesions in Acute Anterior Poliomyelitis.*—Dr. Abercrombie's observations related to the cases of three children. Each of these had sustained a fracture, and at intervals respectively of 11 days, 12 days, and about 20 days became the subject of an attack of acute poliomyelitis. All the fractured limbs sustained an extensive and severe paralysis, whereas the other limbs recovered. He quoted Charcot's cases in which trauma was followed by a chronic anterior poliomyelitis.

Professor Fraser referred to similar cases observed during an epidemic of 300 cases of poliomyelitis in New York, in which the paralysis was not detected until after the limb was taken out of plaster.

Dr. James Taylor had seen similar cases occurring after injury without fracture.

Dr. Judson Bury, Sir A. Garrod, and Dr. Parker joined in the discussion.

2. *Investigations of the Clinical Value of Sanocrysin : a report of work done under the auspices of the Medical Research Council.*—Professor T. R. Elliott presented a collective report on the clinical results of the use of sanocrysin during the last five months at St. Bartholomew's Hospital (Professor Fraser), the London Hospital (Professor Ellis), St. Mary's Hospital (Professor Langmead), St. Thomas's Hospital (Professor Maclean and Dr. G. Herbert), and at University College Hospital.

OF GREAT BRITAIN AND IRELAND

The general reactions to sancocrysin, namely, fever, skin rashes, albuminuria, and loss of weight, were most obvious in patients with severe tuberculous infections, where they sometimes assumed a dangerous character: they were less obvious in mild cases, and were absent in one non-tuberculous control suffering from lymphadenoma. Out of a total of twenty-five cases treated in London there were two deaths that seemed to be attributable to the gold treatment. There were two instances of rapid cure: one of tuberculous peritonitis and one of what appeared to be caseation in the lungs spreading out from hilum glands; the latter, however, was not a fully proved case of pulmonary tuberculosis. The remaining cases of open tuberculous infection of the lungs generally showed some improvement as the result of treatment, though the improvement was not of a strikingly rapid nature, while in two of them the general condition became worse. The use of the anti-tuberculin serum had in several instances been accompanied by severe serum sickness.

The general conclusion of the London observers was that sancocrysin did appear to have a specific effect on tubercle infected tissues, but that knowledge of the right dose and of the type of lesion that should be chosen for treatment was still so imperfect that it was not justifiable to recommend this method of treatment as one for general use by the medical profession.

Professor Lyle Cummins reported on seven cases treated by sancocrysin in South Wales. The cases chosen were relatively mild and showed evidence of resistance, the sort of case which might have done well at a sanatorium. The rapidity of improvement, however, was so great as to be impressive, and would appear to justify the hope that in suitable cases sancocrysin might prove a valuable aid towards cure. All the patients suffered reactions of varying kinds: six had albuminuria, six had rashes, all had fever, and one had stomatitis.

Sir R. Phillip reported on twenty-two cases treated at Edinburgh. He considered the action of the drug resembled in some respects that of tuberculin as regards systemic disturbance and the rash, though lymph glands did not seem to be so much affected by sancocrysin as by tuberculin. Albuminuria was very pronounced and might last ten to fifteen days, or even longer. He was of opinion that the scale of dosage advised by the Copenhagen authorities required revision, and also that investigations for the present should be confined to early cases of tuberculosis, especially in children.

3. *The Pituitary Body and Fat Metabolism*.—Dr. R. Coope and Dr. E. N. Chamberlain (introduced) described experiments on rabbits showing that subcutaneous injections of pituitrin produced temporary fatty infiltration of the liver, due in all probability to the transfer of fat from depots to the liver. This did not occur after injections of 'antuitrin'. They advanced a tentative hypothesis that secretion of posterior lobe of the pituitary is necessary for the transfer of fat in the depots (as in pituitary obesity). The experiments suggest that it would be of value to try the clinical experiment of treating cases of pituitary obesity with repeated subcutaneous injections of pituitrin in gum arabic solution.

4. *Diverticulosis of the Large Intestine*.—Dr. E. I. Spriggs related the results of an investigation of 100 cases of this condition. The diverticula were not due to pressure but to local inflammatory changes probably due to infection. The pelvic colon was the part most commonly affected, and the descending colon the next in order of frequency. He pointed out the very frequent association of diverticulosis with spondylitis deformans (70 per cent. in 100 cases) and with infected teeth. The communication was illustrated by a very interesting series of X-ray photographs.

5. *Relapsing Nodular Non-suppurative Panniculitis showing Phagocytosis of Fat-cells by Macrophages*.—Dr. Parkes Weber related a case in a woman, thin rather than fat, who was subject to fibrositic pains. The attacks of panniculitis were accompanied by slight fever and albuminuria. All the attacks occurred in 1924: the severest affected the arms and legs, resembling somewhat erythema nodosum, but the subcutaneous tissue, not the skin, was chiefly involved. Microscopic examination of one of the nodules showed phagocyte cells surrounding, and sometimes within, the fat globules.

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In the interstitial inflammatory infiltrate were numerous large multinuclear giant-cells, whose cytoplasm, like that of the macrophages (which might be called lipophages), contained fatty granules. Complete recovery followed.

AFTERNOON SESSION. 2 p.m.

A demonstration of clinical cases was given in the rooms of the Royal Society of Medicine.

An important collection of pathological specimens of historical and general interest was also on view.

Dr. E. P. Poulton and Dr. J. H. M. Campbell demonstrated a new apparatus for determining the metabolic rate.

Dr. George Graham demonstrated the Bence Jones protein reactions in the urine of a case of myeloma.

3 p.m.

1. *A further note on Congenital Heart Disease.*—Dr. E. P. Poulton stated that the combination of congenital pulmonary stenosis and deficient septum was very common. In 150 cases of pulmonary stenosis or atresia, in 121 there was deficiency of the septum, in twelve patent foramen ovale, in one patent ductus arteriosus, and in sixteen the septum was entire. As the result of experimental and clinical observations and of three post-mortems the following suggestions were made. In cases of pure stenosis:

- (1) Cyanosis was not extreme and was relieved by oxygen.
- (2) There was great development of the right side of the heart to physical signs and X-rays.
- (3) There was no great increase in the red cell count.

In cases of *stenosis with deficiency of the septum*:

- (1) There was great cyanosis, not relieved by oxygen.
- (2) The heart, though large, retained its normal shape.
- (3) Polycythaemia was marked.

The murmur was always due to the stenosis and not to the deficiency of the septum.

Dr. Gordon drew attention to the alteration of the character of the murmur according to the position of the patient in cases of patent ductus arteriosus.

2. *The Adrenalin Treatment of severe Heart-block.*—Dr. G. A. Sutherland related a case of acute rheumatic infection in a boy of 17, the onset of the attack being marked by symptoms of acute heart-block. Prolonged standstill of the ventricle led to an alarming condition, with all the manifestations of the Stokes-Adams syndrome. The long ventricular pauses were checked at once by the hypodermic administration of adrenalin solution, although the irregular action due to heart-block persisted for some days.

Dr. Starling related a case of heart-block in a syphilitic subject of 59 in which a 10 c.c. dose of 5 per cent. peptone solution brought about a re-establishment of normal rhythm.

Dr. Hay, Dr. Cassidy, and Dr. Herapath had had the same experience as Dr. Sutherland with adrenalin in cases of heart-block.

Dr. Edgecombe, Dr. Poynton, Dr. Hamill, and Dr. Wilkinson further discussed the communication.

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3. *Primary Abscess of the Brain.*—Professor Edwin Bramwell related a case of a female, aged 19, previously healthy, who had complained for a fortnight of intense headache and had vomited. Pulse-rate 60, temperature sub-normal, no papilloedema, no focal brain signs, and no evidence of disease elsewhere. Cerebro-spinal fluid under pressure clear, cells 18 per c.mm. mononuclears, no organisms detected. *Post mortem*—abscess in right frontal lobe and oedema of brain: no primary source of infection found. Streptococci and Pfeiffer bacillus in the pus. He considered the designation 'primary abscess of the brain' was not defensible pathologically, but was employed here to emphasize the fact that the absence of a detectable aetiology did not necessarily exclude abscess.

Professor Hall and Dr. Symonds referred to cases of pneumococcal abscess of the brain and cerebellum, in which no focus was found in the rest of the body.

4. *A case of Polycythaemia, with a suggestion for the treatment of some cases of High Blood-pressure.*—Dr. S. W. Patterson related a case of polycythaemia with high blood-pressure, in which treatment by X-rays and diathermy gave good results. The blood-pressure fell from 240 mm. to 180 mm.

Dr. Parkes Weber said that he had seen the patient and had regarded it as a case of so-called 'polycythaemia hypertonica'—that is, as a case of polycythaemia rubra secondary to high blood-pressure or the cause of the high blood-pressure, and not as a case of splenomegalic polycythaemia (Vaquez-Osler disease), in which, in spite of the high blood viscosity, the blood-pressure was hardly ever notably increased.

Dr. Ryle considered the fall in the blood-pressure in Dr. Patterson's case was due to the fall in the red count. He referred to the effect of administration of phenyl hydrazine, which caused a rapid and marked fall of the haemoglobin content. It probably produced this action by bringing about a destruction of red cells.

Dr. Tidy, Professor Gulland, and Dr. Starling were opposed to X-ray treatment in these cases, especially when a low white count was present.

5. *The Mechanics of the Water-hammer Pulse.*—Dr. J. C. Bramwell stated that in an artificial schema it can be shown that the front of the pulse-wave, like that of a wave on the sea-shore, tended to become steeper in the course of transmission, and that under certain circumstances parts of it actually became so steep that their condition was rendered unstable. When this occurred pre-anacrotic vibrations appeared on the sphygmogram. There was reason to believe that these were analogous to the rapid anacrotic vibrations sometimes present in the human sphygmogram, in cases of free aortic regurgitation, and it was suggested that an important factor in producing the 'water-hammer' character of the pulse was the sudden shock to which the vessel wall was subjected when a large portion of the wave-front suddenly became unstable.

6. *Post-anginal Cardiac Failure.*—Dr. A. Blackhall-Morison attributed both the immediately fatal issue of angina, and later failure, to cardiac shock, acting *per vias nervosas* on the biochemistry of cardiac muscle with effect chiefly on its contractility.

7. *A plea for the Systematic Percussion of the Liver as a guide to the Heart's vigour.*—Dr. Stacey Wilson described methods for percussion of the liver, and was of opinion that variations in the size of the liver dullness might depend on variations in its elasticity.

Dr. Bain, Dr. Gordon, and Dr. Blackhall-Morison discussed various methods of determining the liver dullness.

The Annual Dinner was held at 7.30 for 8 p.m. at the Hotel Victoria. Sir Humphry Rolleston was in the chair. The official guests were the Right Hon. Lord Justice Atkin, Sir St Clair Thomson, and Sir John Bland-Sutton. 127 members and guests were present.

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SATURDAY MORNING SESSION. 10 a.m.

1. *Notes on a case of Rat-bite Fever.*—Dr. J. A. Wright related a case of rat-bite fever in a man. There was recurrent fever at approximately weekly intervals. The incubation period was five days. The shortest incubation period recorded was four days. Treatment by novarsenobillon led to a rapid and complete cure.

Professor Hall compared the course of the temperature in rat-bite fever with that in lymphadenoma.

Dr. Veale, Dr. Tyson, Dr. Gibson, Dr. Hamill, and others related their experiences in cases of rat-bite fever.

2. *The Clinical Significance of Bundle Branch Block.*—Dr. Cowan described the clinical aspects of eleven cases of bundle branch block, and discussed the aetiology of, and the prognosis in, the lesion. It seemed to occur most often in cases of widespread arterial disease in the later periods of life. It was not necessarily fatal in itself, but its presence indicated gross disease in one part of the cardiac muscle, and death often ensued comparatively rapidly from the associated lesions in the heart and elsewhere.

Professor John Hay referred to 25 cases of bundle branch block. Of these eight showed complete heart-block, eight suffered from angina, and two showed auricular fibrillation. He agreed with Dr. Cowan that if a group of cases were taken in which the electro-cardiogram presented a branch bundle lesion the average expectation of life was lowered as compared with a group similar clinically but in which the electro-cardiogram was normal. In a group of 100 cases of angina, eight showed a bundle lesion. In them the average duration of life, in the seven who died from the onset of anginal pain, was a fraction over two years; in anginal patients with a normal electro-cardiogram and who died, it was a little over four years.

Dr. Parkinson, Dr. Herapath, Dr. Cassidy, Professor Bramwell, and Dr. Veale further discussed the communication.

3. Lord Dawson contributed a further report on the case of high blood-pressure in a girl of 21, now 23, communicated by him in 1923. The heart had increased in size, and the radial arteries were rather too palpable but not hard. The urine was always of low specific gravity, of a large amount, and there was occasionally slight albuminuria. The kidney was explored: a portion removed showed an increase of the muscular coats of the arteries, but little, if any, sign of inflammation or degeneration. The chief change was the thickening of the media. He considered the high blood-pressure was due to some metabolic toxin.

Dr. Crichton Bramwell, Dr. Poynton, and others discussed the communication.

4. *Some improvements in the technique of the van den Bergh reaction for Bilirubin in Blood: with a consideration of the present status of the test in Clinical Medicine.*—Dr. J. W. McNee and Dr. C. S. Keeper (introduced) discussed the value of the van den Bergh reaction, which they regarded as the most valuable of the tests in use at present. They emphasized the importance of applying the test only in fresh specimens of blood: it was useless in stale specimens.

Dr. J. W. McNee and Dr. W. A. Perlzweig (introduced) discussed a method of estimating bile acids in blood-serum and bile.

5. *The Cholesterol Content of the Blood and its significance.*—Dr. Mackenzie Wallis described a method of estimating cholesterol in the blood. He stated that the cholesterol content of the blood in health was remarkably constant—0.16 per cent.

6. *Sacralization of the last Lumbar Vertebra.*—Dr. J. H. Abram related a case in a

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female who had sacralization of the last lumbar vertebra, accompanied by local pain and tenderness. Operation four years ago relieved all symptoms. Skiagrams taken before and after operation were exhibited.

Chlorosis.—Dr. Abram referred to a case of abdominal fatty tumour in a woman who had laced herself very tightly to maintain her figure. This was the only example of chlorosis he had seen for fifteen years.

Dr. W. Dixon stated that chlorosis was still common in some Dutch islands, where tight lacing was still the practice.

2 p.m. to 3 p.m.

Demonstration of clinical cases, pathological specimens of historical and general interest, and radiograms.

AFTERNOON SESSION

3 p.m.

1 a, *Cinematograph demonstration of 'Triple Puncture'.*—Sir J. Purves Stewart gave an interesting cinematograph demonstration of 'triple puncture', i. e. lumbar, cisterna, and ventricular puncture, as employed for diagnostic and therapeutic purposes.

Dr. H. Morley Fletcher asked whether Sir James Purves Stewart had employed ventricular puncture to introduce serum in cases of meningococcal meningitis. Sir J. Purves Stuart replied in the negative.

1. *A case of Congenital Auricular Flutter.*—Dr. F. J. Poynton related a case of auricular flutter, of congenital origin, in a boy now aged 2 years and 8 months. The attacks were characterized by screaming, cyanosis, and sweating. The heart-rate was very variable, from 90 to 200. Emotion was the chief factor. Auricular flutter was demonstrated by the electro-cardiogram.

2. *CO₂ tension in Cardiac Dyspnoea.*—Professor Fraser communicated the results of investigations of the CO₂ tension in cases of simple cardiac dyspnoea. These showed that the arterial blood was more alkaline, and that the CO₂ tension in the arterial blood was lowered as compared with the condition on recovery. This appeared to be due to the respiratory centre being stimulated to overaction, so that CO₂ was washed out. The cause of this stimulation was unknown, but it was suggested that this was the essential mechanism in the dyspnoea of heart failure, although in many cases it was masked by the results of disturbances in the lungs or kidneys.

Dr. Poulton and Dr. Campbell discussed the communication.

3. *Latent Antral Infections in Arthritis, Diabetes, and obscure Toxaemia.*—Sir William Willcox emphasized the importance of transillumination and X-ray examination of the antra in cases of arthritis, diabetes, &c., and related cases in illustration.

Sir St Clair Thomson (introduced) agreed that sinus infection was more often overlooked than sepsis of the teeth or tonsils, and might cause many and often unexpected symptoms. Sinus trouble might cause intolerance of tobacco and alcohol.

4. *A case of Syringomyelia, combined with Locomotor Ataxy.*—Dr. Comrie showed sections of the spinal cord from a woman who had syringomyelia and tabes. There was a remarkable cavitation in some of the dorsal posterior roots.

Professor Ashley Mackintosh questioned whether true tabes was present.

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5. *Malignant Endometrioma, with Diffuse Infiltration of the Lungs.*—Dr. A. S. Barnes, with A. P. Thomson and F. W. Lamb (introduced), described a case. The patient, a woman of 28, complained of increasing shortness of breath in 1923. In 1924 she was sent to Switzerland, but became more dyspnoeic. On her return she was cyanotic. Red corpuscles were 6,880,000 per c.c. She died in 1925. Dr. Lamb reported the P.M. findings and the histological features of the case. The lungs showed a most unusual diffuse infiltration of growth secondary to an endometrioma.

Dr. Russell had seen the case during life and gave some further details.

6. *The treatment of Cancer by Emetine and a fresh infusion of Violet Leaves.*—Dr. W. Gordon related his experience. Both these remedies he considered merited a further trial.

